FORMULATION AND *IN-VITRO* EVALUATION OF BILAYER TABLETS OF SUMATRIPTAN SUCCINATE

A Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University

Chennai - 600 032

In partial fulfillment for the award of Degree of

MASTER OF PHARMACY (Pharmaceutics)

Submitted by

N. RAGHAVENDRA ARYA

Register No: 26106016

Under the Guidance of

Mr. A.UMAR FARUKSHA., M. Pharm.

Assistant Professor, Department of Pharmaceutics

ADHIPARASAKTHI COLLEGE OF PHARMACY

(ACCREDITED BY "NAAC" WITH A CGPA OF 2.74 ON A FOUR POINT SCALE AT "B" GRADE)

MELMARUVATHUR - 603 319

OCTOBER- 2012

CERTIFICATE

This is to certify that the research work entitled **"FORMULATION AND *IN-VITRO* EVALUATION OF BILAYER TABLETS OF SUMATRIPTAN SUCCINATE"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **"N.RAGHAVENDRA ARYA (Register No. 26106016)''** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

A. UMAR FARUKSHA, M. Pharm.,
Assistant Professor,
Department of Pharmaceutics,
Adhiparasakthi College of Pharmacy,
Melmaruvathur - 603 319.

Place: Melmaruvathur
Date:

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND *IN-VITRO* EVALUATION OF BILAYER TABLETS OF SUMATRIPTAN SUCCINATE"** the bonafide research work carried out by **"N.RAGHAVENDRA ARYA" (Register No. 26106016)''** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Mr. A.UMAR FARUKSHA,** M. Pharm., Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, during the academic year 2011-2012.

Prof. (Dr.) T. VETRICHELVAN, M. Pharm., Ph.D.,
Principal,
Adhiparasakthi College of Pharmacy,
Melmaruvathur - 603 319.

Place: Melmaruvathur
Date:

Dedicated

To

My beloved parents...

ACKNOWLEDGEMENT

First and foremost, I wish to express my deep sense of gratitude to His Holiness **ARULTHIRU AMMA** for his ever growing Blessings in each step of the study.

I wish to express my sincere thanks to our respected Vice-President**, THIRUMATHI V. LAKSHMI BANGARU ADIGALAR,** ACMEC Trust, Melmaruvathur, for her excellence in providing skillful and compassionate spirit of unstinted support for carrying out this research work.

I would like to thank **GOD** for showing his blessings upon me by providing me this opportunity to excel one step further in life.

I consider myself to be very fortunate to have, **Mr. A.UMAR FARUKSHA, M. Pharm.,** Assistant Professor, Adhiparasakthi College of Pharmacy, and Melmaruvathur, as Guide, who with his dynamic approach boosted my moral, which helped me to a very great extent in the completion of this dissertation. His assurances and advice had helped me in good steady. His guidance, support, enthuses and encouragement, which made the dissertation an educative and interesting experience. I am in short of words to thank him for unlimited patience, freedom of thought, faith and affection bestowed upon me throughout my project work.

I wish to extend my sincere thanks to **Prof. Dr. T. VETRICHELVAN, M. Pharm., Ph. D.,** Principal, Adhiparasakthi College of Pharmacy, Melmaruvathur, for providing invigorating and conductive environment to pursue this research work with great ease.

I express my heartfelt thanks to **Prof Mr. K. SUNDARAMOORTHY, B.Sc., M. Pharm., Prof Dr. S. SHANMUGAM, M.Pharm., Ph.D., Mr. T. AYYAPPAN M. Pharm.,** Department of Pharmaceutics, and other teaching staff and the non-teaching staff **Mrs. S. KARPAGAVALLI, D. Pharm., Mr. M. GOMATHI SHANKAR, D. Pharm.,**

Mrs. THAKSHYANI, D. Pharm., for their valuable help and guidance during the course of my research work.

I am very grateful to our Librarian **Mr. M. SURESH, M.L.I.S.,** for his kind co-operation and help in providing all reference books and literatures for the completion of this project.

I am highly indebted to **SAVAN PHARMACEUTICALS LTD, Hyderabad**, for allowing me to do project. I thank to **Mr. SANJAY** and **Mr. RAFEEQ (M.Pharm)** for his kind obligation in procuring gift sample of Sumatriptan succinate.

I am very thankful to my brother **K.S SREENIVAS, M.Pharm.,** for providing all facilities and assistance during preparation and my friends **M.HEMA** and **G.SUNIL** for helping me to find out the literature review and completion of my project without any disturbances.

I am very grateful to **Ram computers**, for their kind co-operation and help during the typing work of whole dissertation book.

I am thankful to my colleague, my dear friends, for being a great source of help whenever I needed and for sharing their ideas and extending support during the course of study.

Finally, I can hardly find any words enough to express gratitude to **My Parents**, my ever loving, affectionate Family members especially brother and sisters, sister-in-law and Relatives whose tremendous encouragement, support, prayer, and love which has proved to be a real source of inspiration, and will remain so for the life to come, without which it would have been impossible for me to achieve this success.

Above all “Thank you” to the **Almighty,** who has given me this opportunity to extend my gratitude to all those people who have helped me and guided me throughout my life. I bow my head in complete submission before him for the blessings poured on me.

N.RAGHAVENDRA ARYA

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

GG	----	Guar Gum
XG	----	Xanthan Gum
SA	----	Sodium alginate
EC	----	Ethyl Cellulose
UV	----	Ultra Violet
HCl	----	Hydrochloric acid
µg	----	Microgram
λmax	----	Absorption maximum
ml	----	Milliliter
N	----	Normality
mg	----	Milligram
nm	----	Nanometer
FTIR	----	Fourier Transform-Infra Red Spectroscopy
DSC	----	Differential Scanning Calorimetry
cm	----	Centimeter
%	----	Percentage
RH	----	Relative Humidity
USP	----	United State Pharmacopoeia
IP	----	Indian Pharmacopoeia
t	----	Time
PBS	----	Phosphate Buffer Solution
ICH	----	International Conference on Harmonization
w/v	----	weight/volume
gm	----	Grams

RPM	----	Revolutions per Minute
mm	----	Millimeter
S. No.	----	Serial Number
°C	----	Degree Celsius
SD	----	Standard Deviation
DE	----	Dissolution Efficiency
MDT	----	Mean Dissolution Time
Hrs	----	Hours
<	----	Less Than
>	----	More Than

CHAPTER-1

INTRODUCTION

1.INTRODUCTION

(Yie WC.,1992; Rawlins EA.,1992; Lachman L.)

1.1 Introduction to tablets:

For many decades, treatment of acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers.

Drug may be administered by variety of routes but oral administration is adopted wherever possible. It is safest, easiest and most economical route of drug administration. Among the drugs that are administered orally solid oral dosage forms i.e. tablets and capsules represent the preferred class of products.

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically contain the equivalent of several normal doses of drug. The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills. Tablets and capsules on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world.

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer.

1.1.1 Advantages and disadvantages of tablets as dosage forms

(AultonM, Loyd V. Allen)

Tablets are the most popular dosage form used today and therefore there are several advantages associated with their use. However it is also important to highlight the disadvantages associated with their use.

Advantages

- Tablets are convenient to use and are an elegant dosage form.
- A wide range of tablet types is available, offering a range of drug release rates and durations of clinical effect. Tablets may be formulated to offer rapid drug release or controlled drug release, the latter reducing the number of daily doses required (and in so doing increasing patient compliance).
- Tablets may be formulated to release the therapeutic agent at a particular site within the gastrointestinal tract to reduce side effects, promote absorption at that site and provide a local effect (e.g. ulcerative colitis). This may not be easily achieved by other dosage forms that are administered orally.
- Tablets may be formulated to contain more than one therapeutic agent (even if there is a physical or chemical incompatibility between each active agent). Moreover, the release of each therapeutic agent may be effectively controlled by the tablet formulation and design.
- With the exception of proteins, all classes of therapeutic agents may be administered orally in the form of tablets.
- It is easier to mask the taste of bitter drugs using tablets than for other dosage forms, e.g. liquids.
- Tablets are generally an inexpensive dosage form.
- Tablets may be easily manufactured to show product identification, e.g. exhibiting the required markings on the surface.
- The chemical, physical and microbiological stability of tablet dosage forms is superior to other dosage forms.

Disadvantages

- The manufacture of tablets requires a series of unit operations and therefore there is an increased level of product loss at each stage in the manufacturing process.

- The absorption of therapeutic agents from tablets is dependent on physiological factors, e.g. gastric emptying rate.
- The compression properties of certain therapeutic agents are poor and may present problems in their subsequent formulation and manufacture as tablets.
- The administration of tablets to certain groups, e.g. children and the elderly may be problematic due to difficulties in swallowing. These problems may be overcome by using effervescent tablet dosage forms.

1.1.2 Properties of an ideal tablet:

The objective of formulation and fabrication of tablet is to deliver the correct amount of drug in proper form at or over proper time.

- Tablet should be elegant having its own identity and free from defects such as cracks, chips, contamination, discoloration etc.
- It should have chemical and physical stability to maintain its physical integrity over time.
- It should be capable to prevent any alteration in the chemical and physical properties of medicinal agents.
- It should be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.
- An ideal tablet should be able to release the medicaments in body in predictable and reproducible manner.

1.1.3 Different types of Tablets *(Dr P.K. Sahoo)*

(A) Tablets ingested orally:

1. Compressed tablet, e.g. Paracetamol tablet
2. Multiple compressed tablet `
3. Repeat action tablet
4. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet
5. Sugar coated tablet, e.g. Multivitamin tablet
6. Film coated tablet, e.g. Metronidazole tablet
7. Chewable tablet, e.g. Antacid tablet

(B) Tablets used in oral cavity:

1. Buccal tablet, e.g. Vitamin-c tablet
2. Sublingual tablet, e.g. Vicks Menthol tablet
3. Troches or lozenges
4. Dental cone

(c) Tablets administered by other route:

1. Implantation tablet
2. Vaginal tablet, e.g. Clotrimazole tablet

(D) Tablets used to prepare solution:

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)
2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)
3. Hypodermic tablet
4. Tablet triturates e.g. Enzyme tablet (Digiplex)

- **Compressed tablets:** Standard uncoated tablets are manufactured by compression. The general methods are by wet granulation, dry granulation or direct compression, used for rapid disintegration and drug release. Both type of action – systemic effect and local effect.
- **Multiple compressed tablets**: For incompatible components these are:

  Layered tablet:- Either two layered (for two components) or three layered (for three components) tablet.

  Compressed coated type:- Either tablet within a tablet or tablet within a tablet within a tablet. Tablet in this category are usually prepared for two reasons
  - To separate physically or chemically incompatible ingredients.
  - To produce repeat action or prolong action product.
- **Repeat action tablet:** Sugar coated or multiple compressed tablets are used for this purpose .The core tablet is usually coated with shellac or an enteric polymer so that it will not release its drug in stomach but intestine.
- **Delayed action and enteric-coated tablet:** This dosage form is intended to release the drug after some time delay or after the tablet has passed one part of the GIT into another. All enteric coated tablets are type of delayed action tablet but all delayed action tablets are not enteric or not intended to produce enteric action.
- **Sugar coated tablet**: Primary role is to produce an elegant, glossy, easy to swallow, widely utilized in preparing multivitamin and multivitamin mineral

combination. Sugar coating doubled the tablet weight. Now polymers are used with sugar solution.

- **Film coated tablet:** One type of coated tablet in which drug is not required in coating. This is an attractive method within one or two hours. Polymers such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, and colloidal dispersion of ethylcellulose are commonly used. A 30% dispersion of ethyl cellulose is known as aquacoat. Advantage of film coated over sugar coated tablets is better mechanical strength and flexibility of the coating, little increase in tablet weight.
- **Chewable tablet:** These are intended to be chewed in the mouth before swallowing. Used for large tablet of antacid, bitter or foul testing drugs are not suitable for this type tablet.
- **Buccal and sublingual tablet:** These tablets are small, flat and are intended to be held between the cheek and teeth or in cheek pouch (buccal tablet) or below the tongue (sublingual tablet). Drugs used by this route are for quick systematic action. The tablets are designed not to be disintegrated but slowly dissolve.
- **Troches and lozenges:** Used in the oral cavity to exert local effect in mouth and throat. They are commonly used to treat sore throat or to control coughing in common cold. They may contain local **anaesthetics**, **antiseptic**, **antibacterial agents**, **demulcents**, **astringent** and **antitussive**. The tablets are dissolving slowly over a period of 30 minutes.
- **Dental cone:** These tablets are designed to be placed in the empty socket remaining after tooth extraction. Main purpose is to prevent microbial growth in the socket or to reduce bleeding.
- **Implantation tablets**: designed for substances implantation to provide prolonged drug effect from one month to a year, tablets are usually small, cylindrical not more than 8mm length. These methods require special surgical technique for implantation and discontinuation of therapy. Generally used for administration of growth hormone to food producing animal.
- **Vaginal tablets**: These are designed to undergo slow dissolution and drug release in vaginal cavity. Tablets are wide or pear shaped, used to antibacterial, antiseptic and astringent to treat vaginal infection.
- **Effervescent tablets:** Tablets are designed to produce a solution rapidly with the release of carbon dioxide. The tablets are prepared by compressing the active

ingredient with mixture of organic acid such as citric acid or tartaric acid and sodium bicarbonate.

- **Dispersing tablets**: Tablets are intended to be added to a given volume of water to produce a solution of a given drug concentration.
- **Hypodermic tablets:** These tablets are composed of one or more drugs with water-soluble ingredients. Drug is added to sterile water to prepare sterile solution, which is injectable.
- **Tablet triturates:** Usually are made from moist materials using a triturate mold, which gives them the shape of cylinder. Such tablet must be completely and rapidly soluble.

1.2 Techniques to formulate the tablets

(Bentley's, Larry L. Augsburger, Bogner RH.,1997)

Normally tablets are manufactured by any one of the following methods.

- Direct compression
- Granulation

1.2.1 Direct compression:

The process of direct compression is a process of applying pressure via an upper and a lower punch to materials held in die cavity without doing any prior granulation processes.

A compressible vehicle is blended with the medicinal agent, and if necessary, with a lubricant and a disintegrant, and then the blend is compressed. Substances that are commonly used as directly compressible vehicles are: Lactose, Dicalcium phosphate (Emcompress), Spray Dried Mannitol (Pearlitol SD 200), Microcrystalline Cellulose (Avicel), compressible sugar (Di-Pac), Starch (Sta-Rx 1500), Hydrolyzed Starch (Celutab), and a blend of Sugar, Invert sugar, Starch and Magnesium stearate (Nutab).

The following statements are considered main advantages of direct compression method:

- Single process, because the critical steps like granulation, drying or not involved.
- Thermoliabile and moisture sensitive drug can be used in this technique, in which it can't be done in granulation method.

- Energy and cost of manufacturing is less comparative to granulation method.
- Faster dissolution was obtained.

The following statements are considered disadvantages of direct compression method:

- Tablet weight, thickness, hardness uniformity is difficult to achieve.
- Segregation of drug and excipient may occur.
- For the low dose tablets required content uniformity is difficult to achieve.

Table 1: General Direct Compression Tablet formula

Active Pharmaceutical Ingredient	0.1-99%
Filler-binder (Dependent on API loading and compactability)	1-99%
Disintegrant	0.5-2%
Lubricant	0.5-2%

1.2.2 Granulation *(Loyd V. Allen)*

Its part of the pharmaceutical process that attempts to improve the flow of powdered materials by forming spheres like aggregates called granules.

a) Dry granulation

In the dry methods of granulation the primary powder particles are aggregated under high pressure and no liquid is used.

b) Wet granulation

Tabletting by wet granulation process is the most widely used method for pharmaceutical materials. The technique involves a number of stages. During the development of a tablet formulation, all the physical variables that affect the resultant granules have to be also considered to maximize the quality of the final product.

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent, which must be volatile, so that it can be removed by drying and it must be non-toxic.

Typical liquids of Aqueous (or) Non Aqueous Solvents can be used alone or in combination.

The granulation agents may be used alone or usually as a solvent containing a dissolved solvent in turn containing a dissolved adhesive (also referred to as binder (or) binding agent) which is used to ensure particle adhesion when the granule is dry.

1.3 Tablet Ingredients *(Dr P.K. Sahoo)*

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

1. Diluent
2. Binder and adhesive
3. Disintegrants
4. Lubricants and glidants
5. Colouring agents
6. Flavouring agents
7. Sweetening agents

1.3.1. Diluent: Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. Secondary reason is to provide better tablet properties such as improve cohesion, to permit use of direct compression manufacturing or to promote flow. A diluent should have following properties:

1. They must be non toxic
2. They must be commercially available in acceptable grade
3. There cost must be low
4. They must be physiologically inert
5. They must be physically & chemically stable by themselves & in combination with the drugs.
6. They must be free from all microbial contamination.
7. They do not alter the bioavailability of drug.
8. They must be colour compatible.

Commonly used tablet diluents

1. Lactose-anhydrous and spray dried lactose
2. Directly compressed starch-Sta Rx 1500
3. Hydrolyzed starch-Emdex and Celutab

4. Microcrystalline cellulose-Avicel (PH 101and PH 102)
5. Dibasic calcium phosphate dehydrate
6. Calcium sulphate dihydrate
7. Mannitol
8. Sorbitol
9. Sucrose- Sugartab, DiPac, Nutab
10. Dextrose

Lactose: Most widely used diluent in tablet formulation. Lactose has no reaction with most drugs, whether it is used in hydrous or anhydrous form. Anhydrous lactose has advantage over lactose that it does not undergo Maillard reaction which is browning & discoloration of tablet due to the interaction of amine drug with lactose. Spray dried lactose in conc 20-25% of active ingredient is used for direct compression.

Starch obtained from corn, wheat, potatoes is used as diluent, Sta-Rx 1500 is free flowing, direct compressible starch used as diluent, binder and /or disintegrating agent. Two hydrolyzed starch Emdex and Celutab, which are combination of 90-92% of dextrose and 3-5% of maltose, are free flowing and direct compressible.

Sucrose is used as diluent. Some sugar-based diluents are used for direct compression. These are:

a) Sugartab: 90-93% sucrose and 7-10% invert sugar

b) DiPac: 97%sucrose and 3% modified dextrin

c) Nu Tab: 95%sucrose & 4% invert sugar with small amount of corn starch & magnesium stearate.

Microcrystalline cellulose, having trade name Avicel is used for direct compression. These are two types: PH101 (Powder) and PH102 (Granules). Dibasic calcium phosphate and calcium sulphate used as diluents but reduce bioavailability of tetracycline tablet.

1.3.2. Binders and Adhesives: These materials are added either dry or in wet- form to form granules or to form cohesive compacts for directly compressed tablet.

Example: Acacia, tragacanth- Solution for 10-25% Conc.

Cellulose derivatives- Methyl cellulose, Hydroxypropyl methyl cellulose, Hydroxypropyl cellulose

Gelatin- 10-20% solution

Glucose- 50% solution

Polyvinylpyrrolidone (PVP)- 2% conc.

Starch paste-10-20% solution

Sodium alginate

Sorbitol

1.3.3. Disintegrants: Added to a tablet formulation to facilitate its breaking or disintegration when it contact in water in the GIT.

Example: Starch- 5-20% of tablet weight.

Starch derivative – Primogel and Explotab (1-8%)

Clays- Veegum HV, bentonite 10% level in colored tablet only

Cellulose derivatives- Ac- Di-Sol (sodium carboxy methyl cellulose)

Alginate

PVP (Polyvinylpyrrolidone), cross-linked

Super disintegrants: Swells up to ten fold within 30 seconds when contact water.

Example: Croscarmellose- cross-linked cellulose, Crosspovidone- cross-linked povidone (polymer), Sodium starch glycolate- cross-linked starch. These cross-linked products swell upto 10 fold within 30 seconds when in contact with water.

A portion of disintegrant is added before granulation and a portion before compression, which serve as glidants or lubricant. Evaluation of carbon dioxide in effervescent tablets is also one way of disintegration

1.3.4. Lubricant and Glidants: Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.

Example: Lubricants- Stearic acid, Stearic acid salt - Stearic acid, Magnesium stearate, Talc, PEG (Polyethylene glycols), Surfactants

Glidants- Corn Starch – 5-10% conc., Talc-5% conc., Silica derivative - Colloidal silicas such as Cab-O-Sil, Syloid, Aerosil in 0.25-3% conc.

1.3.5. Colouring agent: The use of colours and dyes in a tablet has three purposes:

(1) Masking of off colour drugs

(2) Product Identification

(3) Production of more elegant product

All colouring agents must be approved and certified by FDA. Two forms of colours are used in tablet preparation – FD &C and D & C dyes. These dyes are applied as solution in the granulating agent or Lake form of these dyes. Lakes are dyes absorbed on hydrous oxide and employed as dry powder colouring.

Example: FD & C yellow 6-sunset yellow
FD & C yellow 5- Tartrazine

FD & C green 3- Fast Green

FD & C blue 1- Brilliant Blue

FD & C blue 2 - Indigo carmine

D & C red 3- Erythrosine

D & C red 22 – Eosin Y

1.3.6. Flavouring agents: For chewable tablet- flavour oil are used.

1.3.7. Sweetening agents: For chewable tablets: Sugar, mannitol.

Saccharine (artificial): 500 times sweeter than sucrose

Disadvantage: Bitter aftertaste and carcinogenic

Aspartame (artificial)

Disadvantage: Lack of stability in presence of moisture.

(Darshana HD.,2000; Turner S.,2004; Chien YW.,2010)

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site of the body, to achieve promptly and then maintain the desired therapeutic drug concentration that elicits the desired pharmacological actions and to minimize the incidence and the severity of unwanted adverse effects. To achieve this goal, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, a twice-daily regimen. An appropriately designed extended release dosage form can be a major advance in this direction compared to conventional immediate release dosage forms.

A large number of preparations deliver drugs in immediate release form that are absorbed in the upper regions of the small intestine, an increasingly important group of products frequently referred to as modified, controlled, or extended-release delivery systems are designed to deliver drug in the entire gastrointestinal (GI) tract but always in a controlled manner. The common rationale underpinning all systems is to modulate the magnitude and duration of drug action and to dissociate or modify these from the inherent limitations and properties of the drug molecules.

In recent times, various developed and developing countries move towards combination therapy for treatment of multiple diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects is minimized, a low dose of two different agents reduces the dose related risk, the addition of one agent may potentiate effects of other agent. Using low dosage of two different agents minimizes the clinical and metabolic side effects that occur with maximal dosage of individual component of the combined tablet and thus dose of the single components can be reduced. Bilayer tablets are novel drug delivery systems where combination of two or more drugs in single unit having different release profiles improves patient compliance, prolongs the drugs action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level. Bilayer tablets are very common dosage form for drugs such as captopril, metoprolol, amoxicillin and potassium clavanate, propanolol hydrochloride, bambuterol hydrochloride. Joint national committee VI recognized the value of combination therapy and suggested that combining drugs with different modes of action will often allow smaller doses of drugs to be used to achive control and minimize the potential dose dependent side effects. JNCvi recomended that the combination of a low dose of two drugs in fixed dose combination is an appropriate choice for initial treatment of any chronic disease. Hence management of multiple diseases can be effectively and better done by bilayer tablet or layering tablet.

1.4 Layered tablet: *(Lieberman HA.,2008; Cremer K.,2001)*

Layer tablet is composed of two or three layers of granulation compressed together. They have appearance like as sandwich because the edges of each layer are exposed. This dosage form has the advantage of separating two incompatible substances with an inert

barrier between them. Layer tablet may be bilayer, trilayer or multilayer depending up on the number of layers.

1.4.1 Multi layer tablets:

This tablet consists of two or more layers of materials compressed successively in the same tablets. The colour of each layer may be the same or different. The tablets having layers of different colours are known as multicoloured tablets.

Multilayer tablets are the tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be setup for two or three layers. More are possible but the design become very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

1.4.2 Advantage of multilayer tablets:

This dosage form has the advantage of separating two incompatible substances with an inert barrier between them.

It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release proportion in the second. A third layer, with an immediate release might be added.

The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating. Two layer tablets require fewer materials than compression coated tablets, weigh less, and may be thinner. Monograms and other distinctive markings may be impressed in the surface of the multilayer tablets. Colouring the separate layer provides many possibilities for unique tablet identity. Analytical work may be simplified by the separation of layer prior to assy. Since there is no transfer to a second set of punches and dies, as with the dry coating machine, odd shapes (such as triangle, squares, and ovals) present no operating problems except for those common to keyed tooling.

1.4.3 Problems in layered tablets:

Lack of proper bonding of two layers.

Stress due to high compression force degrades certain actives, e.g; ramipril.

1.4.4 Bilayer tablets: *(Lachman.,2008)*

Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.

1.4.5 Applications:

1. Used in combination therapy.
2. Used to deliver the loading dose and sustained dose of the same or different drugs.
3. Used for bilayer floating in which one layer is floating layer another one is release layer of the drug.
4. Used to deliver the two different drugs having different release profiles.

1.4.6 Advantages:

1. Bilayer tablet is suitable for preventing direct contact of two drugs and thus two maximize the efficacy of combination of two drugs.
2. Patient compliance is enhanced leading to improve drug regimen efficacy.
3. Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.
4. Bilayer tablets can be designed in such a manner as to modify releases as either of the layers can be kept as extended and the other as immediate release.
5. Fixed low-dose combinations are very useful tools for treatment.

1.4.7 Disadvantages:

1. Adds complexity and bilayer rotatary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Inaccurate individual layer weight control.
4. Cross-contamination between the layers.

1.4.8 Ideal properties for bilayer tablet press:

1. Preventing capping and separation of the two individual layers that constitute the bilayer tablet.
2. Preventing cross-contamination between the two layers.
3. Producing a clear visual separation between the two layers.
4. High yield, accurate and individual weight control of the two layers.

1.4.9 Types of bilayer tablet press:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitoring.

1. **Single sided tablet press:** The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of the single sided press:

1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.
3. Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
4. This may be corrected by reducing the turrent-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

2. **Double sided tablet press**: In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

3. **Bilayer tablet press with displacement:** The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied precompression force.

1.4.10 SIZES AND SHAPES: *(Banker G)*

Size is limited by the capacity of the machine with the total thickness being the same as a single-layer tablet. Many shape other than round or possible and or limited only by the ingenuity of the die maker. However, deep concavities can cause distoriation of the layers. Therefore standard concave and flat-face beveled edge tooling make for the best appearance, especially when the layers are of different colours.

1.4.11 GRANULATIONS:

For a good- quality tablets with sharp definition between the layers, special care must be taken as follows…

- Dusty fines must be limited. Fines smaller than 100 mesh should be kept at a minimum
- Maximum granule size should be less than 16 mesh for smooth, scrape –off at the die
- Materials that smear chalk, or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.
- Low moisture is essential if incompatibilities are used.
- Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.
- Formulation of bi layer tablets is more demanding than the single-layer tablets. For this reason selection of additives is critical.

1.5 TABLET BILAYER PRESS

A Tablet bi-layer press is simply a tablet press that has been modified so that it has two die-filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two-layer tablet and a second time for the second layer. Three-layer presses are equipped with three such compression cycles.

There are two types of layer presses presently in use-one in which each layer can be ejected from the press separately for the purpose of weight checking, and the second in which the first layer is compressed so hard that the second layer will not bond to it, or will bond so poorly that upon ejection the layers easily separated for weighing. Once the proper weight adjustments have been made by adjusting the die fill, the pressure is adjusted to the proper tablet hardness and bonding of the layers.

One hazard of layer tablet production is the lack of proper bonding of the layers. This can result in a lot of 100,000, tablets ending up as 200,000 layers after several days if the layers are not sufficiently bonded.

In a two-layer tablet press, two hopers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continuous, gentle circulation of the materials through hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carry over to the second layer and affect the layer weight ,tablet hardness, and, in case of differently coloured granulations , the appearance of the tablet. The same procedure is followed in the three layer press with three hoppers for the granulations instead of two.

Certain single layer or unit tablet presses are equipped with two compression station prior to the final compaction. These high speed productions by increasing dwell time of the material under pressure make tablets harder and denser.

1.5.1 CONVENTIONAL TECHNIQUES FOR PREPARATION OF BILAYERED TABLETS: *(Banker G)*

Bi layered tablets can be prepared by the following methods:

- Tablet moulding
- Direct compression
- Spray drying
- Sublimation
- Freeze drying (or) Lyophilization
- Mass extrusion
- Taste masking
- Use of sugar based excipients

1) Tablet Moulding:

Moulded tablets are usually prepared by different moulding techniques.

A. **Compression moulding:** The powder mixture previously moistened with a solvent like ethanol/water is compressed into mould plates to form a wetted mass.

B**. Heat moulding:** The moulded forms can be obtained directly from a molten matrix in which the drug is dispersed / dissolved.

C. **No vacuum Lyophilization**: In this process at standard pressure the solvent from a drug solution or suspension is evaporated.

Tablets produced by moulding are solid dispersion. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. The tablets prepared by moulding offer more rapid disintegration and improved taste as the dispersion matrix is made from water soluble excipients (sugars).

Moulded tablets typically do not possess great mechanical strength. Erosion and breakage of the moulded tablet often occur during handling and opening of blister packs.

2) Direct Compression

It is the easiest way to manufacture tablets with low cost, conventional equipments, commonly available excipients and a limited number of processing steps leading to this technique is preferable one. High doses can be accommodated and final weight of tablet can easily exceed that of other production methods.

The disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrate, water soluble excipients and effervescing agents. The optimum concentration of superdisintegrant can be selected according to critical concentration of the disintegrate. Below this concentration the tablet disintegration time is inversely proportional to the concentration of superdisintegrant, whereas if concentration of superdisintegrant incorporated in tablet is above the critical concentration, the disintegration time remains approximately constant or even increases.

3) Spray Drying

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated during the process. This technique is based upon a particulate support matrix that is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredient and compressed into tablet, which disintegrated in less than 20 seconds when immersed in an aqueous medium.

4) Sublimation

Compressed tablets composed of water soluble excipients as tablet matrix often do not dissolve rapidly due to low porosity. Bi layer tablets having porous structure and sufficient mechanical strength, which dissolves quickly have been developed using urea, ammonium carbonate, camphor, naphthalene, and tablet excipients and finally compressed the blend. Porous structure is generated by sublimation of volatile oil.

5) Freeze Drying / Lyophilization

A process in which water is sublimated from the product after freezing is called Freeze drying. Lyophilization results in preparations which are highly porous with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

The use of Freeze drying is limited due to high cost of the equipment and processing. Other major disadvantages of the final dosage forms include lack of physical resistance in standard blister packs.

6) Mass Extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

7) Taste Masking

Taste masking is an essential requirement for bi layer Tablets for commercial success. Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers like Eudragit E, Eudragit L-55 and Eudragit RL.

8) Use of Sugar Based Excipients

Sugar based excipients (eg: Sorbitol, mannitol, dextrose, xylitol, fructose etc.) have been used as bulk agents. Aqueous solubility and sweetness impart pleasing mouth feel and good taste masking. But no sugar based materials have fast dissolution rate and good compressibility and/or compatibility. However technologies are developed to make use of the sugar based excipients in the design of bi layer tablet.

1.5.2 Potential reason for considering the double-layer dosage form:

One of the most common reasons that have developed for wishing to manufacture double-layer product centres on sustained release verses immediate release active ingredients and the related bioavailability of each within the human body. It is the intention of the manufacturer in some cases to formulate products that utilize two different actives, one whose pharmacological effect is available to the body shortly after it is ingested (immediate release) and another that fulfils its route more slowly over a long period of time (sustain release). These two functions can be neatly delivered in the same tablet by separating the actives into two distinct layers. Some active ingredient combinations for a tablet may also be better suited to the double layer form if they cannot easily be blended in to the same final formulation. Certain ingredient may simply need to be physically separated due to incompatibility. An example of a characteristic that might foster such incompatibility would be disparate dissolution rates.

Another modern catalyst for utilization of the double-layer form focuses on the idea of product line extension. As patent protection begins to wane manufacturers can sometimes breathe a new life into a product line by modifying its format or presentation. This can in some cases be achieved by creating a double-layer version of what was historically in mono-layer tablet. The best cases may result in a new patent for the revised form, there by extending the life of a product line.

Perhaps the most interesting emerging use for a double-layer tablet focuses on the desire to thwart abuse of a constituent ingredient. Abusers of pharmaceutical preparation have been increasingly successful and inventive in their ability to extract powerful ingredient for use not intended by the manufacture.

Certain new painkillers, for example, provide wonderful benefits to a patient in need who uses them according to the manufacturer instructions. When an abuser mishandles them, however, they can become dangerous and potentially addictive. The makers of some of this type of products are beginning to investigate the use of double-layer forms, where an antagonist layer is formulated in such a way as to foil would be abuser's attempt to extract the active ingredient that they are seeking it abuse.

1.5.3 Solving incompatibility problem:

Not only active ingredients but also excipients may cause incompatibility either with other excipients or with the drug, and thus lead to unsatisfactory product stability. They preferred strategy to avoid such undesirable interaction is to reformulate the product using other excipients rather than designing a layer tablet.

Drug-drug interactions leading to incompatibility are rare. However, even if the problem occurs, it is usually solved by using other strategies, such as isolating one of the drugs by micro encapsulation prior to its incorporation, or by developing hard gelatin capsules which contain two species of pellets with different drugs.

Nevertheless, some products also use layer tablets for the same purpose. One of the most successful formulations of these types is the popular American multivitamin product, Dual Tabs, which contains vitamins in one of its two layers, and mineral salts, betaine, and glutamic acid, some of which would accelerate the decomposition of the vitamins, in the other.

1.5.4 Some novel bilayer and trilayer tablet devices:

(Patra CN.,2007; Sonara GS.,2007; Ohmori S.,2000; Li B.,2007; Fassihi R.,1997;)

A. Sustained release bilayer tablets:

The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast releasing layer and may contain bi-or triple layers to

sustain the drug release. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules lead to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granule. Among the different polymers, Eudragit and ethylcellulose have been used successfully to obtain appropriate sustained release matrix formulations of different materials.

B. Bilayer and floating-bioadhesive tablets:

A bilayer and floating-bioadhesive drug delivery system exhibiting a unique combination of floatation and bioadhesion to prolong residence in the stomach. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotator press. Granules and tablets were characterized using a official method. The kind of the tablet exhibits independent regulation of buoyancy and drug release.

C. Bilayer caplets:

A bilayer caplets are excellent in two respect; firstly, single unit, such as bilayer caplets, excel in unit size than multiple unit, such as spansule capsules, and secondly, tablet shape changes from flat to capsule-like, namely caplets, that improves easiness in swallowing as compared with flat tablets.

D. Tablet in capsule devices:

This novel system is so called tablet in capsule devices. The designed capsule device consists of an impermeable capsule body and a soluble cap. The multi-layered formulation prepared is filled within the capsule body and sealed with the water-soluble cap. Three-layered tablets, which serves as the first two pulses, a two-layered tablet or in powdered forms, which forms the pulsatile drug release. Both multi-layered tablets are inserted into an impermeable capsule body with a water soluble cap, lactose filled in the bottom.

E. Three layered tablet system:

To allow biphasic drug release a three-layer tablet system has been developed. Two layers both contain a drug dose. An outer drug layer contains the immediately available dose of drug. An intermediate, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first

layer can also involve a drug-free hydrophilic polymer barrier providing delayed (5h) drug absorption.

1.5.5 Bilayer problems: *(Vogeleer J.,2002)*

Layer separation.

Insufficient hardness.

Inaccurate individual layer weight control.

Cross contamination between layers.

Reduced yield.

1.5.6 Bi-layer tablets: Quality and GMP-requirement:

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the selected press is capable of:

Preventing capping and separation of the two individual layers that constitute the bilayer tablet.

Providing sufficient tablet hardness.

Preventing cross-contamination between the two layers.

High yield.

Accurate and individual weight control of the two layers.

1.6 MIGRAINE: *(D.K Arulmozhi.,2005; Stephen D.,2006)*

Migraine is a chronic, often debilitating disease that affects 12% of the general population. This episodic brain disorder is characterized by unilateral throbbing headache lasting from 4 h to 3 days. Associated symptoms include nausea vomiting and sensitivity to light, sound and head movements. A working definition of migraine is benign recurring headache and/or neurological dysfunction usually attended by pain-free interludes and often provoked by stereotyped stimuli. Migraine is more common in females, with a hereditary predisposition towards attacks and the cranial circulatory phenomenon appears to be secondary to a primary central nervous system disorder. Migraine apparently a global disorder, occurring in all races, cultures and geographical locations. Current figures

suggest that 18% of women and six percent of men suffer from migraine and those numbers are increasing. The highest incidence of migraine occurs between the ages of 20 and 35 and often associated with a positive family history of the disease.

Migraine is a common episodic pain disorder, the treatment of which can be acute to stop an attack or preventive to reduce the frequency, duration or severity of attacks. Preventive treatment is used when attacks are frequent or disabling. Many different medication groups are used for preventive treatment, including β-blockers, antidepressants and antiepileptic drugs. Their mechanisms of action include raising the threshold to migraine activation, enhancing antinociception, inhibiting cortical spreading depression, inhibiting peripheral and central sensitization, blocking neurogenic inflammation and modulating sympathetic, parasympathetic or 5-HT tone. In this article, I review evidence of the effectiveness of migraine preventive drugs. I also discuss the setting of treatment priorities.

1.6.1 Pathophysiology of migraine: **(***D.K Arulmozhi.,2005)*

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine) attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement and when treated, the attacks typically last 4 to 72 h. A combination of features is required for the diagnosis, but not all features are present in every attack or in every patient. These symptoms do distinguish migraine from tension type headache, the most common form of primary headache, which is characterized by the lack of associated features. Any severe and recurrent headache is most likely a form of migraine and should be responsive to antimigraine therapy. In 15% of patients migraine attacks are usually preceded or accompanied by transient focal neurotic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine). In a recent, large population-based study, 64% of patients with migraine had only migraine without aura, 18% had only migraine with aura and 13% had both types of migraine (the remaining 5% had aura without headache). Thus, up to 31% of patients with migraine have aura on some occasions, but clinicians who rely on the presence of aura for the diagnosis of migraine will miss many cases. A recent survey by the World Health Organization(WHO), rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders. This ranking suggests that in the judgment of WHO, a day with severe migraine is a disabling as a day with quadriplegia.

1.6.2 Theories of migraine:

a) Vascular theory

In the late 1930's, Harold Wolff became the first researcher to place migraine on a scientific basis, Wolf measured the diameter of the extracranial (temporal) arteries in patients suffering migraine attacks and found them to be dilated. These patients were treated with vasoconstrictors (ergotamine) which relieved the pain and decreased the arterial dilation. Although subsequent events leading to headache (and associated symptoms) are not completely understood, the increased vascular pulsation may activate stretch receptors. This would, in turn increase the activity of neuropeptide containing (mainly calcitonin gene-related peptide (CGRP) perivascular nerves which may ultimately cause pain and other associated symptoms. In line with the finding that carotid arteriovenous anastomoses dilatation play a role in the pathogenesis of migraine, it is reasonable to believe that compounds which produce a cranioselective vasoconstriction may have a potential therapeutic use in the treatment of migraine. In anaesthetized dogs and pigs acutely acting antimigraine drugs, ergot alkaloids (ergotamine and dihydroergotamine) and triptans (sumatriptan and second generation triptans) produced potent vasoconstriction in the canine and porcine carotid vasculature. Further studies demonstrated that mainly 5-HT1B receptors mediate sumatriptan- induced cranial vasoconstriction, involving carotid arteriovenous anastomoses and temporal and middle meningeal arteries.

b) Neurological theory

A second theory of migraine is the neurological theory of migraine. This theory suggests that migraine arises as a result of abnormal neuronal firing and neurotransmitter release in brain neurons. This theory focuses on an explanation for certain symptoms, such as premonitory symptoms occurring prior to an attack (prodrome), which are difficult to explain based on the vascular hypothesis. The fact that migraine headaches begin and develop slowly coupled to the fact that external factors, such as stress, and hunger can precipitate migraine attacks to pathologies arising in the neuronal system, thus supporting a neurological basis of migraine. Cortical spreading depression, an expanding depolarization of cortical neurons which is well characterized in many species but not in man is often suggested to underlie the aura or prodrome associated with initiation of migraine attack. During spreading depression, cortical function is disrupted subsequent to neuronal depolarization and increased extracellular potassium. These cortical changes are

thought to be the cause of the transient sensory or motor impairments that frequently proceed the painful period of a migraine attack.

c) Neurogenic theory:

In this it demonstrated that blood flow changes similar to those known to occur in migraine could be produced by electrically stimulating brain stem structures. This finding led to the neurogenic theory. Stimulation studies investigated the relationship between the trigeminal nerve and the cranial vasculature showed that trigeminovascular axons from blood vessels of the pia mater and dura mater release vasoactive peptides producing a sterile inflammatory reaction with pain. During this neurogenic inflammation, the trigeminal ganglion is stimulated and this induces neurogenic protein extravasation. Vasodilatory peptides then released, including calcitonin gene related peptide (CGRP), substance P (SP) and neurokinin A. Neurogenic theory is an attempt to reconcile the vascular changes in the neuronal dysfunction that may occur in migraine headache and proposes that migraine pain is associated with inflammation and dilation of the meninges, particularly the dura, a membrane surrounding the brain. Neurogenic dural inflammation is thought to result from the actions of inflammatory neuropeptides released from the primary sensory nerve terminals innervating the dural blood vessels. In fact, the dural membrane surrounding the brain is the source for the majority of intracranial pain afferents and dural stimulation produces headache like pain in human. Stimulation or inflammation of sensory fibers release the inflammatory neuropeptides, substance P and calcitonin gene-related peptide onto dural tissue, where these peptides produce a local response called neurogenic inflammation. Neurogenic inflammation may lower the nociceptive threshold required to stimulate meningial sensory fibers. According to neurogenic dural inflammation theory of migraine, release of these inflammatory neuropeptides in the dura mater during migraine can act on vascular tissues to cause vasodilatation, plasma protein extravasation in the surrounding area, endothelial changes, platelet aggregation and subsequent release of serotonin and other mediators, white cell adhesion and subsequent inflammation. CGRP plays a facilitatory role in this process. Whereas substance P induces extravasation via activation of NK1 receptors, release of CGRP enhances the effects of substance P by increasing dural blood flow and by inhibiting an extracellular enzyme that normally can metabolize substance P. Therefore, these two sensory neuropeptides act in concert to produce painful dural inflammation. Although not reliably demonstrated, increased cranial venous concentration of CGRP have been observed during a migraine attack and the elevated concentrations of CGRP have returned to normal following

treatment of the migraine in the serotonergic agonists. This theory is in consistent with the proposal that serotonergic agonist alleviate the acute pain of migraine by inhibiting the release of substance P and CGRP from trigeminal sensory afferent neurons surrounding the meninges.

1.6.4 Pain mechanisms in migraine:

The pathogenesis of pain in migraine is not completely understood so far, but three key factors merit considerations are: the cranial blood vessels, the trigeminal innervation of the vessels, and the reflex connection of the trigeminal system in the cranial parasympathetic outflow. The substance of the brain is largely insensate; pain can be generated by large cranial vessels, proximal intracranial vessels or by the dura mater. These vessels are innervated by branches of the ophthalmic division of the trigeminal nerve, whereas the structures of the posterior fossa are innervated by branches of the C2 nerve roots. In nonhuman primates, stimulation of vascular afferents leads to the activation of neurons in the superficial layers of the trigeminal nucleus caudalis in the region of the craniomedullary junction and the superficial layers of the dorsal horns C1 and C2 levels of the spinal cord trigeminocervical complex. Similarly, stimulation of branches of C2 activates neurons in the same regions of the brain. The involvement of ophthalmic division of the trigeminal nerve and the overlap with structures innervated by C2 explain the common distribution of migraine pain over the frontal and temporal regions, as well as involvement of parietal, occipital and high cervical regions by what is, in essence, referred pain. Peripheral trigeminal activation in migraine is evidenced by release of CGRP, a vasodilator, but the mechanism of generation of pain is not clear. Studies in animals suggest that the pain may be caused by a sterile neurogenic inflammatory process in the dura mater, but this mechanism has not been clearly demonstrated to correlate in humans. The pain may be a combination of an altered perception as a result of peripheral or central sterilization of craniovascular input that is not usually painful and the activation of feed-forward neurovascular dilator mechanism that is functionally specific for the first (ophthalmic) division of the trigeminal nerve.

1.6.5 Emerging therapies *(Peterson K.A., 2005; Edvinsson., 2004; Goldstein D.J.,1999)*

a) Calciotonin gene-related peptide (CGRP) antagonists:

In the recent past, there has been an upsurge in CGRP research and its notable role in migraine pathophysiology. As discussed above, migraine headache is closely associated

with the activation of trigeminovascular system. CGRP immunoreactive fibres originating in the trigeminal ganglion innervate cranial cerebral blood vessels. In animals, stimulation of these sensory nerve fibers has been shown to cause antidromic release of CGRP and subsequent vasodilatation in the cerebral vasculature. Plasma concentrations of CGRP in the jugular venous blood, but not of other neuropeptides were elevated during the headache phase of migraine. Furthermore, in migraine patients: (a) strong correlation was found between plasma CGRP concentrations and migraine headache (b) infusion of CGRP produced a migraine-like headache (c) baseline CGRP levels were considerably higher and (d) the changes in plasma CGRP levels during migraine attacks significantly correlated with the headache intensity. Hence, inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine. In line with this concept, an important breakthrough in the field of CGRP is the development of potent CGRP receptor antagonist olcegepant (BIBN4096BS). In the in vivo animal models of migraine, olcegepant attenuated the vasodilation induced by trigeminal stimulation and capsaicin- induced anastomotic dilatation. Data from recently published clinical proof-of-concept study by demonstrated the effectiveness and safety of olcegepant for acute treatment of migraine, in which the response rate was found similar to oral triptans. No cardiovascular side effects have been reported following administration of olcegepant. The lack of cardiovascular side effects may prove to be a major advantage for using CGRP receptor antagonists to treat migraine.

b) Anticonvulsants:

Migraine and epilepsy share several features and respond too many of the same pharmacological agents suggesting similar mechanism may be involved in their pathophysiology, hence new targets are being investigated for the prophylactic therapy of migraine. Amongst these, anticonvulsants as a class of drugs hold promise for the migraine prophylaxis. These drugs are thought to act through multiple mechanisms involving voltage gated ion channels, ligand gated ion channels, GABA (g- amino butyric acid), glutamate etc. In the central nervous system, GABA is a major inhibitory neurotransmitter and known anticonvulsant drugs like sodium valproate, topiramate and gabapentine have been shown to be effective in preventing migraine through modulation of GABA neurotransmission.

c) Histamine H3 agonists:

In recent study, histamine H3 agonists are evaluated for the safety and efficacy for migraine prophylaxis. Hence carefully controlled doses of H3 receptor

agonist may offer an alternative approach to migraine prophylaxis.

d) Botulinum toxin type A:

BoNT-A, produced by the bacterium Clostridium botolinium consists of a heavy chain and light chain linked by a disulfide bond. BoNT-A binds to pre-synaptic nerve terminal and is internalized into the cell, where it inhibits acetylcholine release by interfering with vesicle docking. These effects make BoNT-A useful for the treatment of many disorders related to excessive muscle contraction, such as strabismus, blepharospasm, hemifacial spasm and cervical dystonia. New applications of BoNT-A in pain therapy support a mechanism for pain reduction that is more complex than a simple secondary effect of muscle relaxation. BoNT-A has been used successfully to treat several different types of headaches, including tension type headaches. cervicogenic headaches and migraine. Although some types of headaches may have been relieved by the inhibition of muscle contraction at trigger points, the efficacy of BoNT-A in treating migraine headache implies a direct action on sensory neurons, with an indirect central action. It is believed that release of vasoactive neuropeptides, such as SP and CGRP from the trigeminal nerve onto the vasculature produces vasodilatation and plasma protein extravasation due to increased permeability of post capillary venules. It is proposed that, the effectiveness of BoNT-A for the treatment of migraine in the clinical setting may be due to its inhibition of neurogenic inflammation induced by the peripheral release of SP and CGRP.

e) Coenzyme Q10:

There has been recent interest in the role that mitochondria may play in migraine pathogenesis. It is clear from the recent studies that at least a subset of migraineurs has a dysfunction in mitochondrial energy metabolism. Coenzyme Q10 is an essential element of the mitochondrial electron transport chain. It is naturally occurring, small hydrophobic substance that freely moves throughout the membrane transferring electrons from the NADH dehydrogenase complex and the succinate-Q-reductase complex to cytochrome C. In addition to its actions as an electron carrier, coenzyme Q10 may act as antioxidant and help protect the myocardium from post-ischaemic reperfusion injury. If mitochondrial dysfunction is playing a role in migraine genesis then coenzyme Q10 could improve mitochondrial function and thus prevent migraine headaches. This belief is not without precedence as riboflavin, in an open label study and a placebo-controlled trial has been shown to reduce migraine frequency. Riboflavin is indirectly involved in the electron transport chain as a precursor of flavin mononucleotides. Coenzyme Q10 is an essential

element of the electron transport chain, suggesting that it could also work as migraine preventive.

f) NK-1 receptors:

According to neurogenic inflammation theory of migraine, SP induces dural inflammation and increases sensitization to migraine headache pain by stimulating NK-1 receptors. Lanepitant is a high affinity, non-peptide, competitive NK-1 receptor antagonist that acts both peripherally and centrally and reported to be effective in guinea pig model of dural inflammation. Thus, NK-1 receptor antagonists may have a role in migraine therapy.

g) Nociceptin:

Nociceptin is an endogenous ligand for the opiate-4 (OP- 4) receptor. The OP-4 receptor abundantly expressed in various CNS structures in rodents, nonhuman primates and in humans, supporting the role of nociceptin in multitude of CNS functions, including motor and balance control, reinforcement and reward, nociception, the stress response, sexual behavior, aggression and autonomic control of physiologic processes. It has been reported that approximately 70% of neurons in the human trigeminal ganglion exhibit nociceptin immunoreactivity and express OP-4 receptor mRNA. In these cells nociceptin is co-localized with CGRP and substance P, marker peptides of the trigeminovascular system. This distribution suggests that nociceptin may be involved in the regulation of neuropeptide release from trigeminal nerve terminals and perhaps in migraine. Interestingly, in an animal model nociceptin dose-dependently suppressed the neurogenic dural vasodilatation, while it had no effect on baseline vessel diameter, also in a recent study lower circulating levels of nociceptin was observed during migraine attacks. Hence drugs targeting OP-4 receptor might be a promising alternative in the pharmacological treatment of migraine.

h) Melatonin:

Melatonin is a derivative of essential amino acid tryptophan, synthesized in the pineal gland. It has wide therapeutic implications including sleeping disorders, circadian rhythm, insomnia in blind people, insomnia in elderly patients, aging and Alzheimer disease. It has been observed that some patients reporting their headaches predominantly or specifically at a certain period of the day. Both episodic and chronic migrainers reported waking up in the morning with headaches or being woken up at night by the headache. Also migraine patients without depression had lower levels of melatonin than controls. Since, melatonin is involved in cerebrovascular regulation, treatment of headache

disorders including migraine is promising. Melatonin may also be involved in migraine comorbidity. Insomina in headache patients is the most likely associated condition in migraine to respond to melatonin therapy. However, the data from large human trials are yet come to provide a proof-of-concept for the potential role of melatonin therapy in migraine.

CHAPTER-2

LITERATURE SURVEY

2. LITERATURE SURVEY

2.1. Literature Review:

1. **Bhalala chirag., *et al*. (2012)** formulated bilayer tablets of Metformin HCL and Pioglitazone HCL of which Metformin HCL as sustained release and Pioglitazone HCL as immediate release layer. Sustained layer were prepared by wet granulation method using HPMC K4 as polymer, immediate release layer were prepared by direct compression method using superdisintegrants such as crosscarmellose sodium. In vitro release studies were carried out by USP type 2 paddle apparatus. The result showed that polymer HPMC K4 in sustained layer can control the release of drug. The in vitro release profile of drug from sustained release layer could be expressed by higuchi's equation as pilot show high linearity R2=0.9911and diffusion was the dominant mechanism of drug release. The formulation (F9) having immediate release layer produces immediate effect 94.53±0.30 within 45 minutes followed by sustained release effect (95.77±0.37) upto 8 hours. The present study concluded that Bilayer tablets of Pioglitazone HCL and Metformin HCL can be a better alternative to conventional dosage form for providing sustained drug delivery.
2. **Chinam Niranjan Patra., *et al*. (2007)** developed a bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. In vitro dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. In vitro dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. Statistical analysis (ANOVA) showed no significant difference in the cumulative amount of drug release after 15 min, but significant difference ($p < 0.05$) in the amount of drug released after 12 h from optimized formulations was observed.
3. **Chitra karthikeyini.S., *et al*. (2009)** developed a bilayer tablet of Aceclofenac sodium using superdisintegrant, sodium starch glycolate for the fast release layer

and water immiscible polymers such as Eudragit RL100 for the sustaining layer. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. *In Vitro* dissolution studies were carried out in a USP type II Paddle type apparatus. The formulation gave an initial burst effect and followed by sustained release for 24 hrs. The optimized formulation (F5) showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60º c/80% RH for 3 months. The TG /DTA analysis revealed that there was no significant interaction between polymers and drug .The drug release from F5 Formulation was found to zero order kinetics. It was also found linear in Higuchi's plot which confirms that diffusion is one of the mechanism of drug release .In this study optimized formulation (F5) release the drug upto 24hrs and fulfilled many requirements such as easy to fabricate , cost effective and high patient compliance.

4. **Dhruvita patel., *et al*. (2012)** formulated bilayer tablets containing Metformin HCl in extended release matrix form and Pioglitazone HCl in immediate release form for the treatment of diabetes mellitus. Influence of hydrophilic carrier, hydrophobic polymer on drug release was studied. Immediate release layer of Pioglitazone HCl was optimised using different super disintegrants.All formulations are evaluated for percentage drug release. Optimisation results indicated that release rate of Metformin is directly proportional to the levels of Eudragit S 100 and PEG 6000. Results confirmed that bilayer tablet formulation containing extended release of Metformin HCl and immediate release of Pioglitazone HCl could be developed by using melt granulation technique.
5. **G.Vinoth Kumar., *et al*. (2011)** formulated Bi-layer tablets of Cefixime trihydrate and Dicloxacillin sodium using povidone k-30 as binder. Cefixime is a cephalosporin antibiotic used to treat infections caused by bacteria such as pneumonia, bronchitis, gonorrhea, and ear, lung, throat, and urinary tract infections. Dicloxacillin is a semi synthetic antibiotic which resists destruction by the enzyme penicillinase. It is used to treat different types of infections caused by bacteria such as bronchitis, pneumonia, etc. A total number of nine formulations have been taken to optimize and develop a robust and stable formulation. Wet granulation process was used for the formulation of both layers. Among the formulations tablets of formulation -5 was taken as optimized formula due to its higher rate of dissolution and compiled all the other parameters with the official specifications.

6. **Girish S. Sonar.,** ***et al***. **(2007)** developed a bilayer and fl oating-bioadhesive drug delivery system exhibiting a unique combination of fl oatation and bioadhesion to prolong residence in the stomach using rosiglitazone maleate as a model drug. The sustained layer was compressed and granules of the floating layer were added to it then both layers were compressed using a single station rotary press. Granules and tablets were characterized using the official method. Hydroxypropyl methylcellulose (HPMC) and sodium bicarbonate were added to the floating layer and, when immersed in 0.1 mol/l HCl, the tablet expands and rises to the surface where the drug is gradually released without interference from gas bubbles. The *in vitro* drug release from the tablet was controlled by the amount of HPMC in the sustained release layer. The fl oating ability of the tablets was studied by gamma scintigraphy. The release of rosiglitazone maleate from the tablets followed the matrixfi rst-order release model. The concentration of HPMC signifi cantly affects the drug release rate, buoyancy lag-time, detachment force and swelling characteristics of the tablets. The tablet was buoyant for up to 8 h in the human stomach.
7. **Hosna Banu.,** ***et al*****. (2011)** designed acetaminophen extended release bi layer tablets containing immediate release layer and extended release layer. Tablets were prepared by wet granulation technique using different grades of hydroxypropylmethyl cellulose (HPMC 15 cps, HPMC 100 cps and Methocel K4m CR) as release rate retardant. In vitro release studies were performed using USP type II apparatus (paddle method) in 900 mL of 0.1N HCl at 50 rpm for 4 hours and compared with USP specification. In vitro release studies revealed that the release rate decreased with increase of polymer loading and viscosity. Formulation ER-4 (containing 10% HPMC 100 cps and 1.5% sodium starch glycolate) and ER-6 (containing 1.5% Methocel K4M CR and 0.5% sodium starch glycolate) were found to follow compendia specification for drug release profile. Drug release was analyzed using zero-order, first order, Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the bi layer matrix tablets. Mathematical analysis of the release kinetics indicated that release from the matrix tablets followed Fickian diffusion. So the bi-layer tablets could be a potential dosage form for delivering acetaminophen.
8. **Jain Jitendra.,** ***et al*****. (2011)** developed a bilayer-floating tablet for Indomethacin using direct compression technology. Bilayer tablets were punched using optimized

solid dispersion, HPMC K4M, Avicel PH-112, ac-di-sol, magnesium stearate and aerosil in fast release layer and optimized floating layer as sustained release layer. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. In Vitro dissolution studies were carried out in a USP type II Paddle type apparatus. The optimized formulation (A2) showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60º c/80% RH for 3 months. The release data obtained from the dissolution study of the bilayer tablets were analysed with respect to first order model, Higuchi model, Korsmeyer-Peppas model, and zero order models. In this study optimized formulation (A2) release the drug up to 24hrs and fulfilled many requirements.

9. **Kiran muscle., *et al*. (2011)** formulated bilayer tablet of diclofenac sodium and pracetamol with diclofenac as sustained release formulation. In the same sustained release layer of diclofenac sodium, an immediate layer of paracetamol was optimised separately and then constituted in bilayer tablet using the amount of polyethylene glycol, microcrystalline cellulose and crospovidone as independent variables for fabricating paracetamol tablets. Diclofenac sodium tablets were prepared using hydroxylpropylmethylcellulose as a matrixing agent.
10. **MA Naeem., *et al*. (2010)** developed bilayer tablet formulations of tramadol HCl (TmH) and acetaminophen (AAP) microparticles using Coacervation via temperature change method, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. The microparticles of the two drugs were prepared separately and then compressed into bilayer tablets. The physicochemical compatibility and stability of the tablets were determined by Fourier transform infrared spectroscopy (FTIR), x-ray diffractometry (XRD), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) while their mechanism and pattern of drug release were assessed by applying Higuchi, Zero order, First order and Korsmeyer-Peppas kinetic models. Bilayer tablets were subjected to accelerated stability studies for three months. FTIR, XRD, DSC and TGA data for the formulations indicate good compatibility and stability. Furthermore, accelerated stability studies confirmed the stability of the formulations. Controlled drug release from the microparticles and bilayer tablets was observed for 8 h and 12 h, respectively. The Higuchi model produced the best fit, with regard to release profile, for both drugs, with correlation coefficient (R2) of 0.966 and 0.960 for AAP and TmH, respectively.

11. **Metkar Vishal., *et al.* (2012)** developed bi-layer tablets of lornoxicam, a highly potent nonsteroidal anti-inflammatory drug with short half-life, that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products. Each of the proposed bi-layer tablets is composed of an immediate-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted analgesic effect. Immediate release layer prepared by using dry granulation method in which ac-di sol used as a disintigrant for immediate release of drug, roll compaction of drug with sodium citrate which act as buffering agent and create basic microenvironmental pH inside the tablets favorable to drug release in acidic conditions. Sustained release layer formulated by using HPMC as release retardant, two grades of HPMC that are HPMC K4M and HPMC K100M used to get sustained release profile for 24 hr. various trial batches are taken to get desired release profile. Batch F8 formulate as bilayer tablet in which drug as to sodium citrate ratio taken 1:5 show maximum drug release 24.67 % for 1 hr in immediate release layer and drug release 98 % for 24 hr in sustained release layer is selected as optimized batch of bilayer tablet formulation. All the prepared bilayer tablets showed acceptable physical properties before and after storage.
12. **Modi Foram P., *et al.* (2011)** developed stable cost effective fixed dose combination moisture barrier film coated bilayer tablet of two incompatible drug artesunate and amodiaquine hydrochloride. Artesunate was very moisture sensitive drug so blend of artesunate layer was prepared by dry granulation method and blend of amodiaquine hydrochloride layer was prepared by wet granulation method. The formula of artesunate layer was optimized using 32 factorial designs & using calcium carbonate as basic stabilizing agent. The formula of amodiaquine hydrochloride was optimized using PVPK-30 as a binder. Result of this study suggested that stable artesunate and amodiaquine hydrochloride moisture barrier film coated bilayer tablet could be successfully formulated using calcium carbonate as basic stabilizing agent & instamoistshield as moisture barrier coating material.
13. **Mr. Ashish A Pahade., *et al.* (2010)** developed bilayer sustained release tablet of Isosorbide mononitrate, an anti-anginal organic nitrate vasodilator. The tablets were prepared by wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, and polyox were used, which can

release the drug up to 24hrs in predetermined rate. Binder used was pvp k-30. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied. The invitro release rate profile showed the higher concentration of F6 polymer in tablet.

14. **Narasaiah.,** ***et al.*** **(2010)** formulated floating tablet of sumatriptan succinate by wet granulation method. The prepared tablets were physically characterised and show results within the limit. The in vitro drug release was carried out for 8 hr from that it was concluded that the drug release for all the formulations were followed by zero order kinetics and peppas modelling. The diffusion exponent was found to be non-fickian diffusion mechanism.
15. **Preeti Karwa.,** ***et al.*** **(2011)** designed a bilayer tablet of Zolpidem Tartrate (ZT) for biphasic release and in vitro evaluation of the same. Bilayer tablets comprised two layers, i.e. immediate release and controlled release layer. The immediate release layer comprised croscarmellose sodium as a super disintegrant and the controlled release layer comprised HPMC K100M as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets. *In vitro* dissolution studies were carried out in a USP apparatus I, basket method. HPMC K100M extended the release of drug from the extended release layer for 6 hr. FTIR studies revealed that there was no interaction between the drug and polymers used in the study. The release of Zolpidem Tartrate was found to follow a pattern of Korsmeyer-Peppas, with Quasi-Fickian diffusion. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. There were no changes observed in physicochemical properties and drug release pattern of tablets. Biphasic drug release pattern was successfully achieved through the formulation of bilayer tablets in this study.

16. **R.Natarajan.,** ***et al.*** **(2011)** formulated Antihypertensive drugs of the Telmisartan and Hydrochlorothiazide immediate release Bilayer tablet, and to study the dissolution profile with the reference product. The Formulation development work was initiated with Wet granulation. Telmisartan is converted to its sodium salt by dissolving in aqueous solution of Sodium Hydroxide, in order to improve solubility and drug release. Lactose Monohydrate and Microcrystalline Cellulose are used as diluents. Starch paste is prepared in Purified Water and is used as the binder. Sodium Starch Glycolate is added as a disintegrating agent. Magnesium Stearate is

used as the lubricant. The prepared granules are compressed into Double layer compression machine. The tablets thus formulated with higher proportion of sodium starch glycolate showed satisfactory physical parameters, and it was found to be stable and in-vitro release studies are shown that formulation (F-T5H5) was 101.11% and 99.89% respectively. And the formulation T5H5 is further selected and compared with the release profile of innovator product, it was found to be similar (f2 factor) to that of marketed product.

17. **R.T. Jadhav.,** ***et al.*** **(2011)** formulated Bi-layer tablets of Piracetam and Vinpocetine, so that synergistic effect of this combination could be used for the effective treatment of Alzheimer Disease. Wet granulation process was used for the formulation of both layers and the final film coated tablets were evaluated for the thickness, weight variation, hardness, friability, disintegration time, dissolution study. Among the formulation, tablets of batch V2 of vinpocetine & batch P3 of piracetam was taken as optimized formula due to its higher rate of dissolution and complied all the other parameters with the official specifications. The stability study of the selected formulations was done at 40°C and 75% RH for 3 months. It was concluded that Piracetam, Vinpocetine Bi-layer tablets can be prepared successfully as it satisfies all the criteria as a Bilayered tablet and would be alternative to the currently available conventional tablets.
18. **Remya P.N.,** ***et al.*** **(2010)** developed a robust formulation of bilayered tablets of Ibuprofen and methocarbamol using povidone k-30 as binder. The mechanism of methocarbamol is a skeletal muscle relaxant which acting centrally through inhibiting inter neuronal activity and blocking polysynaptic reflex pathway at spinal card. Ibuprofen is a pain relieving agent which inhibits the activity of Cyclooxygenase an enzyme crucial for synthesis of prostaglandins. A total number of nine formulations have been taken to optimize and develop a robust and stable formulation. Wet granulation process was used for the formulation of both layers. Among the formulations tablets of formulation -8 was taken as optimized formula due to its higher rate of dissolution and compiled all the other parameters with the official specifications.
19. **S. Jayaprakash.,** ***et al.*** **(2011)** formulated bilayer tablets of Amlodipine besilate (IR) Metoprolol succinate (SR) for the management of hypertension. In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and was directly compressed. For sustained release

portion HPMC polymers were used in granulation stage and also extragranularly. Preformulation studies were performed prior to compression. The compressed bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and invitro drug release using USP dissolution apparatus type 2 (paddle). It was found that the optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol succinate in 1, 4, 8, 20 hours respectively. However, Amlodipine besilate released 98.28% at the end of 30 minutes. The IR spectrum and DSC studies revealed that there is no disturbance in the principal peaks of pure drugs Metoprolol succinate and Amlodipine besilate. This further confirms the integrity of pure drugs and no incompatibility of them with excipients. The stability studies were carried out for the optimized batch for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

20. **Sharmin Rahman., *et al*. (2012)** formulated bilayer tablets of tramadol hydrochloride by direct compression technique incorporating an immediate release layer and a sustained release layer. An immediate release layer was successfully designed to release the bolus dose instantaneously. Water soluble Xanthan gum, water insoluble Kollidon SR and Eudragit L 100 were used as carriers in the sustained release layer of the matrix tablet. The *in vitro* drug release was studied for eight hour, first two hours dissolution in acidic medium followed by six hour dissolution in buffer medium. Matrix tablet showed a sustained release rate with a controlled fashion as a function of the quantity of polymer used. The *in vitro* drug release data were fitted with several mathematical models and mean dissolution time along with fractional dissolution time values (T25%, T50% and T80%) were calculated. Xanthan gum was found to be the most effective rate retarding agent compared to Kollidon SR and Eudragit L 100, when used at same ratio in the formulations.
21. **Supriya S. Shidhaye., *et al.* (2008)** developed and optimized formulations of mucoadhesive bilayered buccal patches of sumatriptan succinate using chitosan as the base matrix and was prepared by the solvent casting method. Gelatin and polyvinyl pyrrolidone (PVP) K30 were incorporated into the patches, to improve the film properties of the patches. The prepared patches were evaluated for

different parameters and it was concluded that the permeation can be increased through the buccal mucosa by using different penetration enhancers.

22. **Yelanki., *et al*. (2010)** developed the sumatriptan nasal mucoadhesive minitablets using different mucoadhesive polymes like chitosan, carbopol 971p, gum copal and HPMC K4M with different ratios and evaluated for thickness, hardness, swelling index, mucoadhesion strength and in vitro drug release. It was observed that the tablets shows controlled release of drug upto 7days and the release data was fit into different kinetic models.

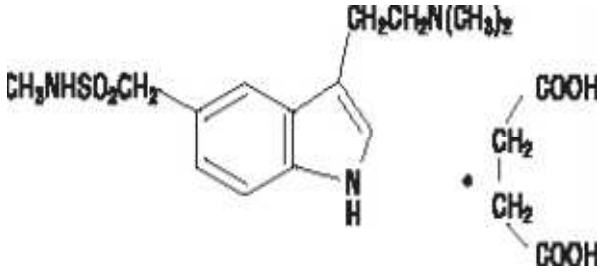
2.2 DRUG PROFILE

(SweetmanSC(Eds), Matrindale.,2002; Neil IM(Eds).,2001; Goodman and Gilman)

SUMATRIPTAN SUCCINATE:

Sumatriptan succinate is 3-[2-(dimethyl amino) ethyl]-*N*-methyl-1H-indole-5-methane sulfonamide succinate. It is 5-HT_1receptor agonist used in the treatment of migraine.

Structure :



IUPAC Name : [3-[2-(Dimethylamino)ethyl]-1H-indole-5-yl]-N-methylmethanesulphonamide hydrogen butanedioate.

Formula : $C_{18}H_{27}N_3O_6S$

Molecular mass : 413.5

Drug category : Anti-migraine agents, Selective Serotonin agonists, Serotonin agonists, Vasoconstrictor agents.

Indication : For the treatment of migraine attacks with or without aura

Bioavailability : 15% (oral) and 96% (s.c)

Half life : 2.5 hours

Protein binding : 14%-21%

Melting point : 166-171 ^oC

Description : White or almost white powder.

Solubility : Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

PHARMACOLOGY:

Mechanism of action: The 5-HT_{1B} and 5-HT_{1D} receptors function as autoreceptors, which inhibit the firing of serotonin neurons and a reduction in the synthesis and release of serotonin upon activation. After sumatriptan binds to these receptors, adenylate cyclase activity is inhibited via regulatory G proteins, increases intracellular calcium, and affects other intracellular events. This results in vasoconstriction and inhibtion of sensory nociceptive (trigeminal) nerve firing and vasoactive neuropeptide release.

Pharmacokinetics:

Absorption: Sumatriptan is rapidly but incompletely absorbed when given orally and undergoes first pass metabolism, resulting in a low absolute bioavailability.

Metabolism: It is extensively metabolised in the liver predominantly by monoamine oxidase type A. Sumatriptan and its metabolite also appear in the faces, small amounts of sumatriptan are distributed in breast milk.

Excretion: Sumatriptan is excreted mainly in the urine as the inactive indole acetic derivative and its glucuronide.

Pharmacodynamics: Sumatriptan, an antimigraine drug, is a selective agonist of vascular serotonin ((5-hydroxytryptamine; 5-HT) type 1-like receptors, likely the 5-HT_{1D} and 5-HT_{1B} subtypes. It has no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT2, 5-HT3 receptor subtypes or at alpha1-, alpha2- or beta-adrenergic; dopamine1; dopamine2; muscarinic; or benzodiazepine receptors.

Toxicity: Symptoms of overdose include convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation.

Indications: For the treatment of migraine attacks with or without aura in adults. Sumatriptan is an antimigraine drug structurally similar to serotonin. It is thought that the cerebral blood vessel constriction induced by activation of 5HT1 receptors on those vessels may contribute to the antimigranious effect of sumatriptan in humans.

Side effects: Rare cardiac events have been associated with the administration of 5-HT1 agonists including coronary artery vasopasm, atrial and ventricular arrhythmias and myocardial infarction. Large doses of sumatriptan can cause sulphahemoglobinemia a rare condition in which the blood changes from red to greenish black due to the integration of sulphur into the haemoglobin molecule.

Contraindications:

- Patients with a known hypersensitivity to sumatriptan or any of the tablet excipients.
- Patients who have had myocardial infarction or have ischaemic heart disease, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease or patients who have symptoms or sign consistent with ischaemic heart disease.
- Patients with a history of cerebrovascular accident (CVA) or transient ischaemic attack (TIA).
- Patients with severe hepatic impairment.
- Patients with moderate and severe hypertension and mild uncontrolled hypertension.
- Concomitant administration of ergotamine or derivatives of ergotamine (including methysergide) is contraindicated.
- Concurrent administration of monoamine oxidase inhibitors and sumatriptan is contraindicated.
- Sumatriptan tablets must not be used within two weeks of discontinuation of therapy with monoamine oxidase inhibitors.

Special warnings and precautions for use:

- Sumatriptan tablets should only be used where there is a clear diagnosis of migraine.
- Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.
- The recommended doses should not be exceeded. As with other migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.
- It should be noted that migraineurs may be at risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischaemic attack).
- Following administration, sumatriptan can be associated with transient symptoms including chest pain and tightness which may be intense and involve the throat. Where such symptoms are thought to indicate ischaemic heart disease, no further doses of sumatriptan tablets should be given and appropriate evaluation should be carried out.

- Sumatriptan tablets should not be given to patients with risk factors for ischaemic heart disease without prior cardiovascular evaluation. Special consideration should be given to postmenopausal women and males over 40 with these risk factors. These evaluations however, may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.
- Sumatriptan tablets should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.
- There have been rare post-marketing reports describing patients with weakness, hyper-reflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.
- Sumatriptan tablets should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of drugs, e.g. impaired hepatic or renal function.
- Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold, as seizures have been reported in association with sumatriptan (see section 4.8)
- Patients with known hypersensitivity to sulphonamides may exhibit an allergic reaction following administration of sumatriptan tablets. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross-sensitivity is limited but caution should be exercised before using sumatriptan in these patients.
- Undesirable effects may be more common during concomitant use of triptans and herbal preparations containing St Johns wort *(Hypericum perforatum).* These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- As with other acute migraine treatments, chronic daily headache/exacerbation of headache have been reported with overuse of sumatriptan, which may necessitate a medicinal product withdrawal.

Interaction with other medicinal products and other forms of interaction:

- Studies in healthy subjects show that sumatriptan does not interact with propranolol, flunarizine, pizotifen or alcohol. Sumatriptan has the potential to interact with MAOIs, ergotamine and derivatives of ergotamine. The increased risk of coronary vasospasm is a theoretical possibility and concomitant administration is contraindicated.
- Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, 24 hours should elapse before sumatriptan tablets can be taken following any ergotamine-containing preparation. Conversely, ergotamine-containing preparations should not be taken until 6 hours have elapsed following administration.
- Rarely, an interaction may occur between sumatriptan and SSRIs.
- There may be a risk of serotonergic syndrome also if sumatriptan is used concomitantly with lithium.

2.3 EXCIPIENT PROFILE

(Raymond CR)

2.3.1 GUAR GUM:

1. Nonproprietary Names:

- BP: Guar galactomannan
- PhEur: Guar galactomannanum
- USPNF: Guar gum

2. Synonyms:

E412; Galactosol; guar flour; jaguar gum; Meyprogat; Meyprodor; Meyprofin.

3. Chemical Name and CAS Registry Number:

Galactomannan polysaccharide [9000-30-0]

4. Empirical Formula and Molecular Weight:

$(C_6H_{12}O_6)_n$ =220 000

5. Structural Formula:

Guar gum consists of linear chains of (1→4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D-mannose is between 1:1.4 and 1:2..

6. Functional Category:

Suspending agent, tablet binder, tablet disintegrant and viscosity increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Guar gum is a galactomannan, commonly used in cosmetics, food products, and pharmaceutical formulations. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose.

In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant, in oral and topical products as a suspending, thickening, and stabilizing agent; and also as a controlled-release carrier. Guar gum has also been examined for use in colonic drug delivery. Guar-gum-based three-layer matrix tablets have been used experimentally in oral controlled-release formulations.

8. Description:

The USPNF 23 describes guar gum as a gum obtained from the ground endosperms of Cyamopsis tetragonolobus (L.) Taub. (Fam. Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, composed of galactan and mannan units

combined through glycoside linkages, which may be described chemically as a galactomannan. The PhEur 2005 similarly describes guar galactomannan as being obtained from the seeds of Cyamopsis tetragonolobus (L.) Taub. by grinding the endosperms and subsequent partial hydrolysis.

The main components are polysaccharides composed of D-galactose and D-mannose in molecular ratios of 1:1.4 to 1:2. The molecule consists of a linear chain of β-(1→4)-glycosidically linked manno-pyranoses and single α-(1→6)-glycosidically linked galacto-pyranoses. Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a bland taste.

9. Typical Properties:

Acidity/alkalinity: pH = 5.0–7.0 (1% w/v aqueous dispersion)

Density*:* 1.492 g/cm^3

Solubility: Practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5–9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.

Viscosity (dynamic): 4.86 Pa s (4860 cP) for a 1% w/v dispersion. Viscosity is dependent upon temperature, time, concentration, pH, rate of agitation, and particle size of the guar gum powder.

10. Stability and Storage Conditions:

Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions.

The bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of 0.15% methylparaben and 0.02% propylparaben as a preservative. In food applications, benzoic acid, citric acid, sodium benzoate, or sorbic acid may be used.

Guar gum powder should be stored in a well-closed container in a cool, dry place.

11. Incompatibilities:

Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum. However, the addition of borate ions to hydrated guar gum produces cohesive structural gels and further hydration is then prevented. The gel formed can be liquefied by reducing the pH to below 7, or by heating.

2.3.2 XANTHAN GUM:

1. Nonproprietary Names:

- BP: Xanthan gum
- PhEur: Xanthani gummi
- USPNF: Xanthan gum

2. Synonyms:

Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural.

3. Chemical Name and CAS Registry Number:

Xanthan gum [11138-66-2]

4. Empirical Formula and Molecular Weight:

$(C_{35}H_{49}O_{29})_n$ Approximately 2×10^6

The USPNF 23 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium salt.

5. Structural Formula:

Each xanthan gum repeat unit contains five sugar residues: two glucose, two mannose, and one glucuronic acid. The polymer backbone consists of four β-D-glucose units linked at the 1 and 4 positions, and is therefore identical in structure to cellulose. Trisaccharide side chains on alternating hydroglucose units distinguish xanthan from cellulose. Each side chain comprises a glucuronic acid residue between two mannose units. At most of the terminal mannose units is a pyruvate moiety; the mannose nearest the main chain carries a single group at C-6. The resulting stiff polymer chain may exist in solution as a single, double, or triple helix that interacts with other xanthan gum molecules to form complex, loosely bound networks.

6. Functional Category:

Stabilizing agent; suspending agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients, and has good stability and viscosity properties over a wide pH and temperature range. Xanthan gum gels show pseudoplastic behavior, the shear thinning being directly

proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

When xanthan gum is mixed with certain inorganic suspending agents, such as magnesium aluminum silicate, or organic gums, synergistic rheological effects occur. In general, mixtures of xanthan gum and magnesium aluminum silicate in ratios between 1:2 and 1:9 produce the optimum properties. Similarly, optimum synergistic effects are obtained with xanthan gum: guar gum ratios between 3:7 and 1:9.

Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Controlled-release tablets of diltiazem hydrochloride prepared using xanthan gum have been reported to sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate.

Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the precorneal area.

Recent studies have revealed that xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.

Xanthan gum can be used to increase the bioadhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems.

Xanthan gum is also used as a hydrocolloid in the food industry, and in cosmetics it has been used as a thickening agent in shampoo.

8. Description:

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

9. Typical Properties:

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution.

Freezing point: 0°C for a 1% w/v aqueous solution.

Heat of combustion: 14.6 J/g (3.5 cal/g)

Melting point: chars at 270°C.

Particle size distribution: various grades with different particle sizes are available; for example, 100% less than 180 μm in size for Keltrol CG; 100% less than 75 μm in size for Keltrol CGF; 100% less than 250 μm, 95% less than 177 μm in size for Rhodigel; 100% less than 177 μm, 92% less than 74 μm in size for Rhodigel 200.

Refractive index: n^{20}_{D} = 1.333 for a 1% w/v aqueous solution.

Solubility: practically insoluble in ethanol and ether; soluble in cold or warm water.

Specific gravity: 1.600 at 25°C

Viscosity (dynamic): 1200–1600 mPa s (1200–1600 cP) for a 1% w/v aqueous solution at 25°C.

10. Stability and Storage Conditions:

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases.

The bulk material should be stored in a well-closed container in a cool, dry place.

11. Incompatibilities:

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution.

Under highly alkaline conditions, polyvalent metal ions such as calcium cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant. The presence of low levels of borates (<300 ppm) can also cause gelation. This may be avoided by increasing the boron ion concentration or by lowering the pH of a formulation to less than pH 5. The addition of ethylene glycol, sorbitol, or mannitol may also prevent this gelation.

Xanthan gum is compatible with most synthetic and natural viscosity-increasing agents. If it is to be combined with cellulose derivatives, then xanthan gum free of cellulase should be used to prevent depolymerization of the cellulose derivative.

The viscosity of xanthan gum solutions is considerably increased, or gelation occurs, in the presence of some materials such as ceratonia, guar gum, and magnesium aluminum silicate. This effect is most pronounced in deionized water and is reduced by the presence of salt. This interaction may be desirable in some instances and can be exploited to reduce the amount of xanthan gum used in a formulation; Xanthan gum solutions are stable in the presence of up to 60% water-miscible organic solvents such as acetone, methanol, ethanol, or propan-2-ol. However, above this concentration precipitation or gelation occurs.

Xanthan gum is incompatible with oxidizing agents, some tablet film-coatings, carboxymethylcellulose sodium, dried aluminum hydroxide gel, and some active ingredients such as amitriptyline, tamoxifen, and verapamil.

2.3.3 SODIUM ALGINATE:

1. Nonproprietary Names:

- BP: Sodium alginate
- PhEur: Natrii alginas
- USPNF: Sodium alginate

2. Synonyms:

Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

3. Chemical Name and CAS Registry Number:

Sodium alginate [9005-38-3]

4. Empirical Formula and Molecular Weight:

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

The block structure and molecular weight of sodium alginate samples has been investigated.

5. Functional Category:

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

6. Applications in Pharmaceutical Formulation or Technology:

Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; it has been used as a diluent in capsule formulations. Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions.

In topical formulations, sodium alginate is widely used as a thickening and suspending agent in a variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions.

Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic-solvent systems. It has also been used in the formation of nanoparticles.

The adhesiveness of hydrogels prepared from sodium alginate has been investigated and drug release from oral mucosal adhesive tablets, and buccal gels, based on sodium alginate

has been reported. Other novel delivery systems containing sodium alginate include ophthalmic solutions that form a gel *in situ* when administered to the eye; an *in situ* forming gel containing paracetamol for oral administration; and a freeze-dried device intended for the delivery of bone-growth factors.

Hydrogel systems containing alginates have also been investigated for delivery of proteins and peptides.

Therapeutically, sodium alginate has been used in combination with an H_2-receptor antagonist in the management of gastroesophageal reflux, and as a hemostatic agent in surgical dressings. Alginate dressings, used to treat exuding wounds, often contain significant amounts of sodium alginate as this improves the gelling properties. Sponges composed of sodium alginate and chitosan produce a sustained drug release and may be useful as wound dressings or as tissue engineering matrices

Sodium alginate is also used in cosmetics and food products.

7. Description:

Sodium alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder.

8. Typical Properties:

Acidity/alkalinity: pH ≈7.2 for a 1% w/v aqueous solution.

Solubility: practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Viscosity (dynamic): various grades of sodium alginate are commercially available that yield aqueous solutions of varying viscosity. Typically, a 1% w/v aqueous solution, at 20°C, will have a viscosity of 20–400 mPa s (20–400 cP). Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions. Above pH 10, viscosity decreases.

9. Stability and Storage Conditions:

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature.

Aqueous solutions of sodium alginate are most stable at pH 4–10. Below pH 3, alginic acid is precipitated. A 1% w/v aqueous solution of sodium alginate exposed to differing temperatures had a viscosity 60–80% of its original value after storage for 2 years. Solutions should not be stored in metal containers.

Sodium alginate solutions are susceptible on storage to microbial spoilage, which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although filtration using a 0.45 μm filter also has only a slight adverse effect on solution viscosity. Heating sodium alginate solutions to temperatures above 70°C causes depolymerization with a subsequent loss of viscosity. Autoclaving of solutions can cause a decrease in viscosity, which may vary depending upon the nature of any other substances present. Gamma irradiation should not be used to sterilize sodium alginate solutions since this process severely reduces solution viscosity.

Preparations for external use may be preserved by the addition of 0.1% chlorocresol, 0.1% chloroxylenol, or parabens. If the medium is acidic, benzoic acid may also be used.

The bulk material should be stored in an airtight container in a cool, dry place.

10. Incompatibilities:

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5%. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations cause salting-out of sodium alginate; salting-out occurs if more than 4% of sodium chloride is present.

2.3.4 CROSPOVIDONE:

1. Nonproprietary Names:

- BP: Crospovidone
- PhEur: Crospovidonum
- USPNF: Crospovidone

2. Synonyms:

Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

3. Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight:

$(C_6H_9NO)_n$ >1 000 000

The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of *N*-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

5. Functional Category:

Tablet disintegrant.

6. Applications in Pharmaceutical Formulation or Technology:

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

7. Description:

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

8. Stability and Storage Conditions:

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

9. Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

2.3.5 STARCH:

1. Nonproprietary Names:

- BP: Maize starch
- Potato starch
- Rice starch
- Tapioca starch
- Wheat starch
- JP: Corn starch
- Potato starch
- Rice starch
- Wheat starch
- PhEur: Maydis amylum (maize starch)
- Solani amylum (potato starch)
- Oryzae amylum (rice starch)
- Tritici amylum (wheat starch)
- USPNF: Corn starch
- Potato starch
- Tapioca
- Wheat starch

2. Synonyms:

Amido; amidon; amilo; amylum; *Aytex P*; C*PharmGel; *Fluftex W*; Instant Pure-Cote; *Melojel*; Meritena; *Paygel 55*; Perfectamyl D6PH; Pure-Bind; Pure-Cote; Pure-Dent; Pure-Gel; Pure-Set; Purity 21; Purity 826; *Tablet White.*

3. Chemical Name and CAS Registry Number:

Starch [9005-25-8]

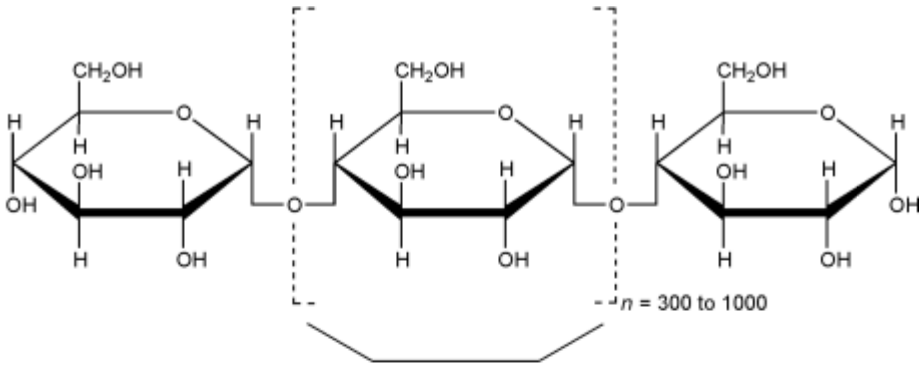
4. Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)_n$ 50 000–160 000

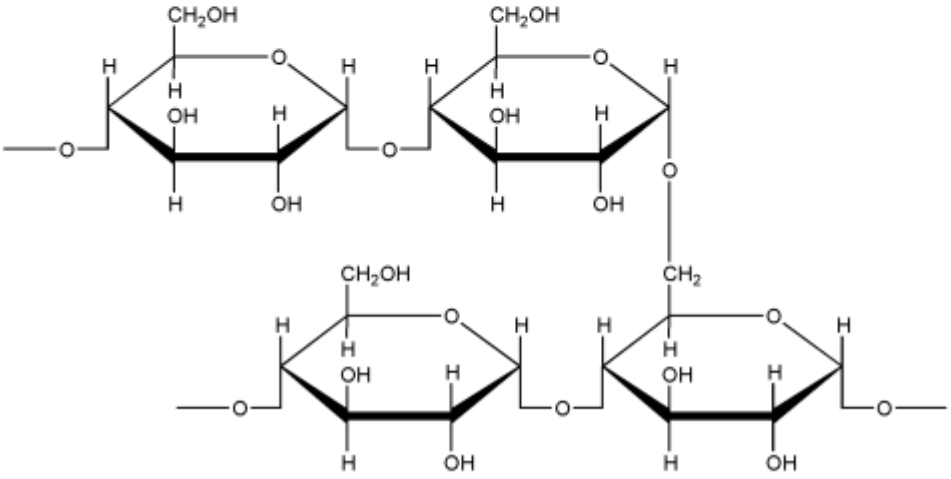
Where n = 300–1000.

Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose.

5. Structural Formula:



Amylose Glucose unit



Segment of amylopectin molecule

6. Functional Category:

Glidant; tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

7. Applications in Pharmaceutical Formulation or Technology:

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

As a diluent, starch is used for the preparation of standardized triturates of colorants or potent drugs to facilitate subsequent mixing or blending processes in manufacturing

operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix.

In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Selection of the quantity required in a given system is determined by optimization studies, using parameters such as granule friability, tablet friability, hardness, disintegration rate, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15% w/w. However, unmodified starch does not compress well and tends to increase tablet friability and capping if used in high concentrations. In granulated formulations, about half the total starch content is included in the granulation mixture and the balance as part of the final blend with the dried granulation. Also, when used as a disintegrant, starch exhibits type II isotherms and have a high specific surface for water sorption.

Starch has been investigated as an excipient in novel drug delivery systems for nasal, oral, periodontal, and other site-specific delivery systems.

Starch is also used in topical preparations; for example, it is widely used in dusting powders for its absorbency, and is used as a protective covering in ointment formulations applied to the skin. Starch mucilage has also been applied to the skin as an emollient, has formed the base of some enemas, and has been used in the treatment of iodine poisoning.

Therapeutically, rice starch-based solutions have been used in the prevention and treatment of dehydration due to acute diarrheal diseases.

8. Description:

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

9. Stability and Storage Conditions:

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties. Starch should be stored in an airtight container in a cool, dry place.

2.3.6 MAGNESIUM STEARATE:

1. Nonproprietary Names:

- BP: Magnesium stearate
- JP: Magnesium stearate
- PhEur: Magnesii stearas
- USPNF: Magnesium stearate

2. Synonyms:

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

3. Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ 591.34

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.

5. Structural Formula:

$[CH_3(CH_2)_{16}COO]_2Mg$

6. Functional Category:

Tablet and capsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

8. Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

9. Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

Flash point: 250°C

Flowability: poorly flowing, cohesive powder.

Melting range:

- 117–150°C (commercial samples);
- 126–130°C (high purity magnesium stearate).

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; s lightly soluble in warm benzene and warm ethanol (95%).

Specific surface area: 1.6–14.8 m^2/g

10. Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

11. Incompatibilities:

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

2.3.7 TALC:

1. Nonproprietary Names

- BP: Purified talc
- JP: Talc
- PhEur: Talcum
- USP: Talc

2. Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

3. Chemical Name and CAS Registry Number:

Talc [14807-96-6]

4. Empirical Formula and Molecular Weight:

Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminum silicate and iron.

5. Functional Category;

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

6. Applications in Pharmaceutical Formulation or Technology:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbant.

In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.

Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

7. Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

8. Typical Properties:

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.

Hardness (Mohs): 1.0–1.5

Moisture content: talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Particle size distribution: varies with the source and grade of material. Two typical grades are ≥99% through a 74 μm (#200 mesh) or ≥99% through a 44 μm (#325 mesh).

Refractive index: n^{20}_{D} = 1.54–1.59

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8

Specific surface area: 2.41–2.42 m^2/g

9. Stability and Storage Conditions:

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.

Talc should be stored in a well-closed container in a cool, dry place.

10. Incompatibilities:

Incompatible with quaternary ammonium compounds.

CHAPTER-3

AIM AND OBJECTIVES

3. AIM AND OBJESTIVES

AIM OF THE STUDY

The primary Aim of the study is modified release of drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. If the drug is given in conventional dosage form, it has to be administered several times a day to produce the desired therapeutic effect. Because of the frequent dosing fluctuation in plasma drug level occurs. If the drug dosing interval is not in accordance with biological half-life large peaks and valleys are possible with time-drug concentration in blood curve. The pronounced fluctuations resulting from the conventional drug administration are likely to yield period of no therapeutic effect when drug concentration fall below minimum therapeutic level.

OBJECTIVE OF THE STUDY

The main objective of present study is to develop Bilayer tablets of Sumatriptan succinate for the treatment Migrainic attacks.

CHAPTER-4

PLAN OF WORK

4. PLAN OF WORK

- **Literature survey**.
- **Materials and equipments.**
- **Preformulation studies.**
  - **Characterization of Drug.**
    - Appearance
    - Melting Point Determination.
    - Solubility Study.
  - **Identification of Drug**
    - FTIR.
    - UV Spectral analysis
  - **Drug - Polymers Interaction Studies.**
    - Differential Scanning Calorimetry (DSC) Analysis.
    - Fourier transforms Infra-Red (FTIR) Spectroscopy Study.
  - **Preparation and Evaluation of Granules.**
    - Bulk density.
    - Tapped density.
    - Carr's Compressibility Index.
    - Hausner's ratio.
    - Angle of repose.
- **Formulation of Bilayer Tablets.**
- **Evaluation of Tablets.**
  - **Physico-Chemical Properties of Tablets.**
    - Appearance.
    - Size and Thickness.
    - Hardness.
    - Friability.
    - Weight variation.
    - Drug content.

- ❖ ***In-vitro*** **Drug Release Studies.**
- ❖ **Kinetics of *In-vitro* drug release**
- ❖ **Stability Studies.**

- ➢ **Results and Discussion.**
- ➢ **Summary and Conclusion.**
- ➢ **Future Prospects.**
- ➢ **Bibliography**

CHAPTER-5

MATERIALS AND EQUIPMENTS

5. MATERIALS AND EQUIPMENTS

5.1 List of Materials used with Sources:

Table 2: List of Materials and their Suppliers.

S. No.	Name of Material	Supplied by
1	Sumatriptan succinate	SAVAN PHARMACEUTICALS
2	Sodium alginate	SAVAN PHARMACEUTICALS
3	Xanthan gum	SAVAN PHARMACEUTICALS
4	Guar gum	SAVAN PHARMACEUTICALS
5	Magnesium stearate	SAVAN PHARMACEUTICALS
6	Microcrystalline cellulose	SAVAN PHARMACEUTICALS
7	Starch	SAVAN PHARMACEUTICALS
8	Talc	SAVAN PHARMACEUTICALS
9	Crospovidone	SAVAN PHARMACEUTICALS

5.2 List of Equipments used with model:

Table 3: List of equipments with their make and model.

S. No.	Name of the equipment	Source
1	Electronic balance	BL- 220H, Shimadzu Corporation , Japan
2	UV-Visible spectrophotometer	Shimadzu-1700, Shimadzu Corporation, Japan
3	Tablet Punching Machine	Remik Equipments, Ahmedabad.
4	Fourier-transformed infrared(FTIR) Spectrophotometer	Perkin elmer-Pharmaspec-1,Japan.
5	Tap density apparatus	Indolabs, Chennai
6	Dissolution test apparatus	ElectroLab, Mumbai
7	Digital pH meter	Elico Scientifics-LI 612, Mumbai.
8	Hot air oven	Lawrence & Mayo.
9	Vernier Caliper	Mitutoyo, Japan.
10	Friability apparatus	Veego corporation
11	Melting point test apparatus	Precision scientific co., Chennai
12	Monsanto Hardness tester	Secor India.

CHAPTER-6

PREFORMULATION STUDIES

6. PREFORMULATION STUDIES

6.1 CHARACTERIZATION OF DRUG:

6.1.1 Colour and Appearance: *(United State Pharmacopoeia, 2007)*

The sample was observed visually.

6.1.2 Melting Point:

Melting point of drug was determined by Melting point test apparatus.

6.1.3 pH Determination:

A 2 % saturated solution of Sumatriptan succinate was prepared in distilled water and pH was measured by digital pH meter.

6.1.4 Solubility: *(Indian Pharmacopoeia, 1996)*

Solubility study was carried out as per the I.P.2007. In this maximum amount of solvent required to dissolve the solute was determined.

6.1.5 Spectral Analysis of Sumatriptan succinate:

6.1.5.1 UV Spectral Analysis of Sumatriptan succinate:

6.1.5.1.1 UV Spectral Analysis of Sumatriptan succinate in 0.1N HCl:

6.1.5.1.1.1 Determination of absorption maximum in 0.1N HCl:

The absorption maximum of the standard solution was scanned between 200-400 nm regions on Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum represented.

6.1.5.1.1.2 Preparation of Standard Curve of Sumatriptan succinate in 0.1N HCl:

Preparation of 0.1N HCl:

0.1N HCl was prepared by diluting 8.5 ml of hydrochloric acid in 1000 ml of distilled water.

Procedure:

Accurately weighed 100mg of Sumatriptan succinate was dissolved in little quantity of 0.1NHydrochloric acid and volume was adjusted to 100ml with the same to prepare a standard solution having concentration of 1000µg/ml. From this above solution 1 ml was pipette out and transferred to a 10 ml volumetric flask and the volume was adjusted with 0.1NHydrochloric acid to a concentration of 100µg/ml. From this stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml was pipette out and transferred to 10 ml volumetric flasks and final volume was made with 0.1NHydrochloric acid for giving concentrations ranged from 2.0 to 10 µg/ml. The absorbance of these solutions was measured in UV-Visible spectrometer at 227nm using 0.1NHydrochloric acid as blank.

Assay of Sumatriptan succinate:

Accurately weighed 25 mg of Sumatriptan succinate was dissolved in little quantity of 0.1N HCl and volume was adjusted to 25 ml with the same to prepare standard solution and the volume was adjusted with 0.1N HCl to get a concentration of 1000µg/ml. From this stock solution, 0.1ml was pipette out and transferred to 10 ml volumetric flask and final volume was adjusted with 0.1N HCl. Absorbance values of these solutions were measured against blank at 227 nm using UV-Visible spectrophotometer. The percentage purity of drug was calculated by using calibration graph method.

6.1.5.1.2 UV Spectral Analysis of Sumatriptan succinate in pH 6.8 phosphate buffer:

6.1.5.1.2.1 Determination of absorption maximum in pH 6.8 phosphate buffer:

The absorption maximum of the standard solution was scanned between 200-400 nm regions on Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum represented.

6.1.5.1.2.2 Preparation of Standard Curve of Sumatriptan succinate in pH 6.8 phosphate buffer:

Preparation of pH 6.8 phosphate buffer :

pH 6.8 phosphate buffer:

50ml of 0.2M potassium dihydrogen phosphate was taken in 200ml volumetric flask, to which 22.4ml of 0.2M sodium hydroxide solution was added and the volume was made upto the mark with distilled water.

0.2M potassium dihydrogen phosphate:

27.218 gm of potassium dihydrogen phosphate was added to 1000ml volumetric flask containing distilled water and the volume was made upto the mark with distilled water.

0.2M Sodium Hydroxide:

8gm of Sodium Hydroxide was taken in a 1000ml volumetric flask containing distilled water and volume was made upto the mark with distilled water.

Procedure:

Accurately weighed 100mg of Sumatriptan succinate was dissolved in little quantity of pH 6.8 phosphate buffer and volume was adjusted to 100ml with the same to prepare a standard solution having concentration of 1000µg/ml. From this above solution 1 ml was pipette out and transferred to a 10 ml volumetric flask and the volume was adjusted with pH 6.8 phosphate buffer to a concentration of 100µg/ml. From this stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml was pipette out and transferred to 10 ml volumetric flasks and final volume was made with pH 6.8 phosphate buffer for giving concentrations ranged from 2.0 to 10 µg/ml. The absorbance of these solutions was measured in UV-Visible spectrometer at 227nm using pH 6.8 phosphate buffer as blank.

6.1.6 Infrared Spectrum: *(Robert M. Silverstein, 2003)*

The infrared spectrum of Sumatriptan succinate was recorded by using FTIR (Perkin elmer-Pharmaspec-1) instrument. A small quantity of sample was mixed with equal quantity of potassium bromide and placed in sample cell to record its IR spectra.

6.1.7 LOSS ON DRYING: *(Indian Pharmacopoeia, 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

6.2 DRUG - POLYMERS COMPATABILITY STUDIES:

Drug polymers studies holds great importance in designing a formulation In drug formulation it is essential to evaluate the possible interactions between the active principle and the polymers, as the choice of the polymers should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product.

6.2.1 Fourier Transform Infra-Red Spectroscopy (FTIR) Study:

(Robert M. Silverstein, 2003; Becket A. H., 2005)

Sumatriptan succinate powder was mixed with various polymers in the ratio of 1:1. Then, afterwards the samples were scanned with FTIR (Perkin Elmer-Pharmaspec-1) over a wave number range of 4000-400 cm^{-1}.

6.2.2 Differential Scanning Calorimetry Study (DSC): *(Jain N. K., 2006)*

Sumatriptan succinate powder was mixed with various polymers in the ratio of 1:1. The mixture of drug with polymers to maximize the like hood of obscuring an interaction. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 10^0C/minute) on DSC. Over a temperature range, which will encompass any thermal changes due to the mixture of drug with polymers thermograms of pure drug are used as a reference.

Appearance or disappearance of one or more peaks in thermograms of drug with polymer are considered as an indication of interaction.

6.3 PREPARATION AND EVALUATION OF POWDER BLENDS:

6.3.1 PREPARATION OF POWDER BLENDS:

All ingredients were weighed and passed through mesh #40 separately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend is passed through mesh # 20 and used for evaluation of flow characteristics.

6.3.2 EVALUATION OF MICROMERITIC PROPERTIES OF POWDERS

- **Angle of Repose:** *(Aulton M.E., 2007; Sinko P. J., 2006; Ansel S. C.,)*

The angle of repose was determined by the funnel method. The accurately weighed (10 gms) granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of granules. The granules were allowed to flow through the funnel freely onto a clean surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where h is the height of granules cone and r is the radius of the granules cone.

Table 4: Relationship between Angle of Repose (θ) and Flowability

S. No.	Angle of repose(θ)	Flowability
1	<20	Excellent
2	20 – 30	Good
3	30 – 35	Passable
4	>40	Very poor

- **Bulk Density and Tapped Bulk Density:**

An accurately weighed (10 gms) granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the granules was measured which give bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave

the tapped volume. Both Bulk Density (BD) and Tapped Bulk Density (TBD) of granules were determined using the following formulae.

BD = Weight of the granules/Volume of the granules

TBD = Weight of the granules/Tapped volume of the granules

- **Carr's Compressibility Index:**

The compressibility index of the granules was determined using following Carr's compressibility index formula.

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the Table 5.

Table 5: Relationship between % Compressibility and Flowability

S. No.	% Compressibility	Flowability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	poor
5	33-38	Very poor
6	>40	Very very poor

- **Hausner's ratio:**

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.25 shows poor flow of granules.

Table 6: Relationship between Hausner's ratio and Flowability

S. No.	Hausner's ratio	Flow Property
1	0.0 - 1.25	Free flow
2	1.25 - 1.6	Cohesive flow

CHAPTER-7

FORMULATION OF SUMATRIPTAN SUCCINATE BILAYER TABLETS

7. FORMULATION OF BILAYER TABLETS

7.1 Formulation development of Sumatriptan Succinate IR layer

Table 7: Formulation development of Sumatriptan Succinate IR layer

S.No	Ingredients	Formula (mg)
1.	Sumatriptane Succinate	50
2.	Crosspovidone	5
3.	Methyl crystalline cellulose	20
4.	Mannitol	20
5	Magnesium Stearate	3
6	Talc	2

7.2 Formulation development of Sumatriptan Succinate SR layer

Table 8: Formulation development of Sumatriptan Succinate SR layer

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sumatriptane Succinate	200	200	200	200	200	200	200	200	200
Xanthan Gum	50			100			25	25	
Guar gum		50			100		25		25
Sodium alginate			50			100		25	25
Starch	40	40	40	40	40	40	40	40	40
Talc	3	3	3	3	3	3	3	3	3
Mannitol	94	94	94	44	44	44	94	94	94
Megnisium stearate	5	5	5	5	5	5	5	5	5
PVP (2%)	8	8	8	8	8	8	8	8	8

7.3 FORMULATION AND CHARACTERIZATION OF BILAYER TABLETS:

(Preeti et al 2011)

The bilayer tablets of Sumatriptan succinate were prepared by the direct compression method. The drug and polymers for both IR and SR layer were passed through a # 60 sieve before their use in the formulation.

Formulation of the IR Layer:

The IR ingredients (Table 7) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies.

Formulation of the SR Layer

The SR ingredients (Table 8) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies.

Compression of Bilayer Tablet

In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed amount of SR powder mix was fed manually into die cavity. SR layer was compressed at mild compression force. After that accurately weighed IR powder mix was manually fed into the die on SR layer and compressed using 8-mm flat punches (Rimek mini press-1 Karnavati Engineering Ltd, Gujarat).

7.4 Dose Calculation:

For sustained drug release up to 24 hr, the immediate dose of drug was calculated from total dose of Sumatriptan succinate extended release tablet.

$$D\text{t} = \text{Dose}\ (1 + 0.693 \times t/t_{1/2})$$

Where,

Dt = Total dose,

Dose = Immediate release dose,

t = Total time period for which sustained release is required,

$t_{1/2}$ = Half-life of drug.

CHAPTER-8

EVALUATION OF SUMATRIPTAN SUCCINATE BILAYER TABLETS

8. EVALUATION OF BILAYER TABLETS

- **Evaluation of Tablets:**

  - **Physico-Chemical Properties of Tablets.**
    - Appearance
    - Thickness
    - Hardness
    - Friability
    - Weight variation
    - Drug content

  - ***In-vitro* Drug Release.**
  - **Kinetics of *in-vitro* drug release.**
  - **Stability Studies.**

8.1 Physico-Chemical Properties of Tablets:

8.1.1 Appearance : *(Lachman L., 1991; Gilbert S., 2007)*

The tablets were visually observed for any capping, chipping and lamination.

8.1.2 Size and Thickness:

The size and thickness of tablet can vary with no change in weight due to difference in Density of granulation, the pressure applied to the tablets and speed of the tablet compression machine. The thickness of the tablets was determined using a Vernier caliper. Three tablets from each type of formulation were used and average values were calculated.

8.1.3 Hardness:

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. Hardness tester (Monsanto tester) was used to measure hardness of tablets. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be taken as a zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

8.1.4 Friability:

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for four minutes, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as follows,

% Friability = (Initial weight - Final weight / Initial weight) x 100.

8.1.5 Weight Variation: *(Indian Pharmacopoeia, 2007)*

The weight variation test is done by taking 20 tablets randomly and they were weighed individually. The composite weight divided by 20, provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by % deviation allowed and none should deviate by more than twice its percentage.

Table 9: Specifications of % weight variation allowed in Tablets as per Indian Pharmacopoeia

Average Weight of Tablet	% Deviation allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

8.1.6 Drug Content:

20 tablets of each formulation taken and amount of drug present in each tablet was determined. Powder equivalent to 25 mg was taken and added in 25 ml of 0.1N HCl followed by stirring for 10 min. This was filtered through a 0.45 µ membrane filter, diluted to get 10 µg/ml concentration and absorbance of resultant solution was measured by UV at 227nm using 0.1N HCl.

8.2 *In-vitro* Dissolution of Tablets:

The release rate of sumatriptan succinate from bilayer tablets was determined using USP Dissolution Testing Apparatus type-I (basket method; Veego Scientific VDA-8DR, Mumbai, India). A sample (5 ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were

filtered through a 0.45µ membrane filter and diluted to a suitable concentration with respected medium. Absorbance of these solutions was measured at 227nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were calculated by using PCP disso V3 software.

***IN-VITRO* DISSOLUTION STUDIES:**

For Sumatriptan Succinate IR Layer:

Medium : 900 ml of 0.1N Hydrochloric acid

RPM : 50

Apparatus : Basket

Time : 15,30,45,60,120 minutes

Wave Length : 227 nm

Temperature : $37^0C \pm 0.5^0C$

For Sumatriptan Succinate SR Layer:

Medium : 900 ml of buffer pH 6.8

RPM : 50

Apparatus : Basket

Time : 4^{th}, 6^{th}, 8^{th}, 12^{th},24^{th} Hours.

Wave Length : 227 nm

Temperature : $37^0 C \pm 0.5^0C$

8.3 Kinetics of *In-vitro* Drug Release: *(Brahmankar D.M., 2006)*

To study the release kinetics of *In-vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

- **Zero order:** $C = K_0 t$

K_0 - zero-order rate constant expressed in units of concentration/time, t - time in hrs.

- **First order:** $LogC = LogC_0 - Kt / 2.303$

Where C_0 - is the initial concentration of drug, K - first order constant, t - time in hrs.

- **Higuchi:** $Qt = Kt^{1/2}$

Where Q_t - amount of the release drug in time t, K- kinetic constant, t- time in hrs.

- **Korsmeyer Peppas:** $Mt / M\infty = Kt^n$

Where M_t - represents amount of the released drug at time t,

M_∞- is the overall amount of the drug (whole dose) released after 24 hrs

K- is the diffusional characteristic of drug/ polymer system constant

n- is a diffusional exponent that characterizes the mechanism of release of drug.

8.4 STABILITY STUDIES: *(Janes T., 2000)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products" describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

Stability studies were carried out at 40°C / 75% RH for the optimized formulation for 3 months. The tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1, 2 and 3 months. The samples were analyzed for its hardness, drug content and *In-vitro* drug release.

CHAPTER-9

RESULTS AND DISCUSSION

9. RESULTS AND DISCUSSION

9.1 CHARACTERIZATION OF DRUG:

9.1.1 Colour and Appearance:

The drug (Sumatriptan succinate) colour is "White to almost white powder" as same as the reported reference.

9.1.2 Melting Point:

The Melting point of Sumatriptan succinate was found to be 169 ± 1.081. The reported melting point of Sumatriptan succinate is 166-171^{0}C. Hence, observed values are complies with USP.

9.1.3 Solubility study:

Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

9.1.4 SPECTROSCOPIC STUDIES:

9.1.4.1 UV Spectroscopy:

9.1.4.1.1 Determination of λmax and Preparation of Calibration Curve of Sumatriptan succinate by using 0.1N HCl:

UV absorption spectrum of Sumatriptan succinate in 0.1N HCl shows λmax at 227nm. Absorbance obtained for various concentrations of Sumatriptan succinate in 0.1N HCl are given in Table 10. The graph of absorbance versus concentration for Sumatriptan succinate was found to be linear in the concentration range of 2-10 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-10 µg /ml.

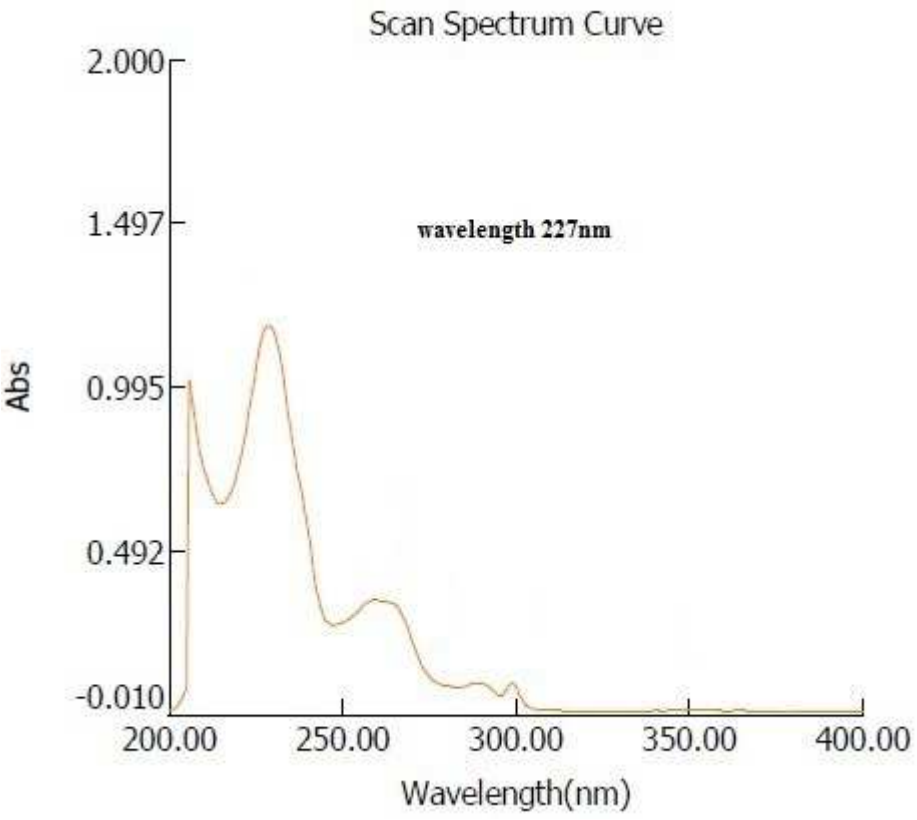


Fig 1: Absorption maximum of Sumatriptan succinate in 0.1N HCl

Table 10: Concentration and Absorbance data for Calibration Curve of Sumatriptan succinate in 0.1 N HCl:

S. No.	Concentrations(µg/ml)	Absorbance at 227nm.
1	0	**0**
2	2	**0.135**
3	4	**0.251**
4	6	**0.367**
5	8	**0.480**
6	10	**0.594**

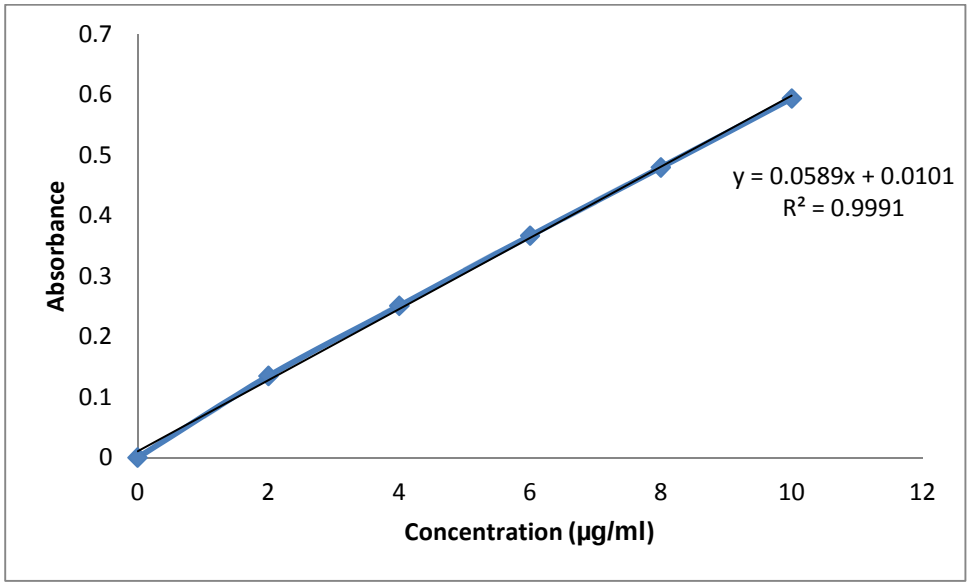


Fig 2: Calibration Curve of Sumatriptan succinate in 0.1 N HCl

UV Spectroscopy:

9.1.4.1.2 Determination of λmax and Preparation of Calibration Curve of Sumatriptan succinate by using pH 6.8 phosphate buffer:

UV absorption spectrum of Sumatriptan succinate in pH 6.8 phosphate buffer shows λmax at 227.8nm. Absorbance obtained for various concentrations of Sumatriptan succinate in pH 6.8 phosphate buffer are given in Table 11. The graph of absorbance versus concentration for Sumatriptan succinate was found to be linear in the concentration range of 2-10 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-10 µg /ml.

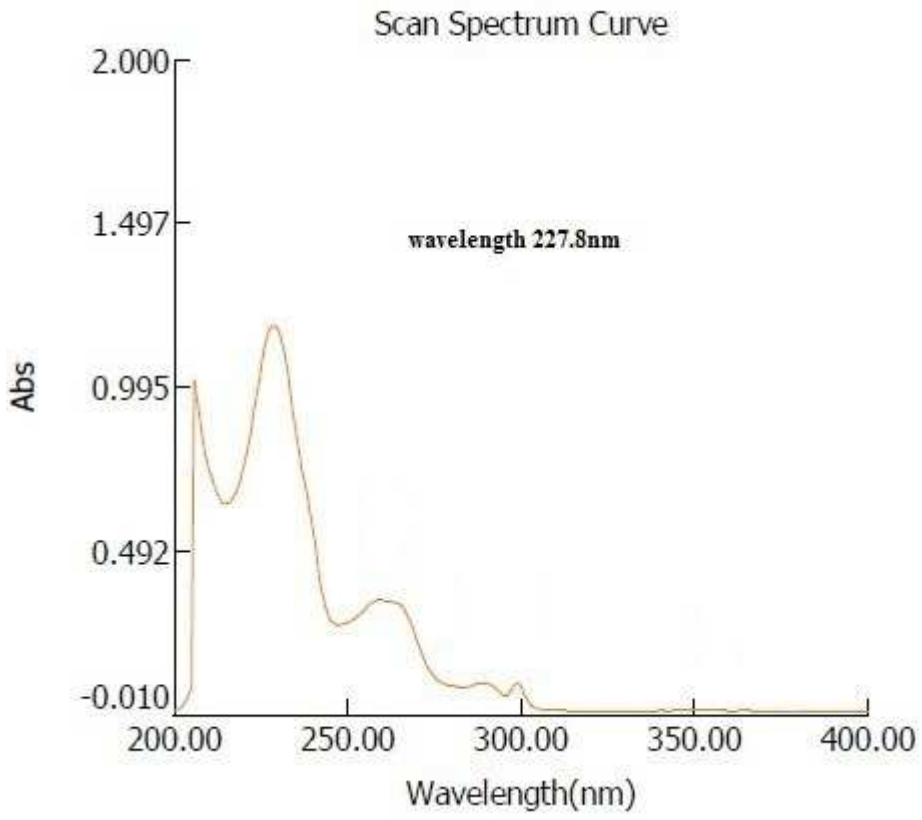


Fig 3: Absorption maximum of Sumatriptan succinate in pH 6.8 phosphate buffer

Table 11: Concentration and Absorbance data for Calibration Curve of Sumatriptan succinate in pH 6.8 Phosphate buffer:

S. No.	Concentrations(µg/ml)	Absorbance at 227.8nm.
1	0	**0**
2	2	**0.145**
3	4	**0.305**
4	6	**0.445**
5	8	**0.604**
6	10	**0.734**

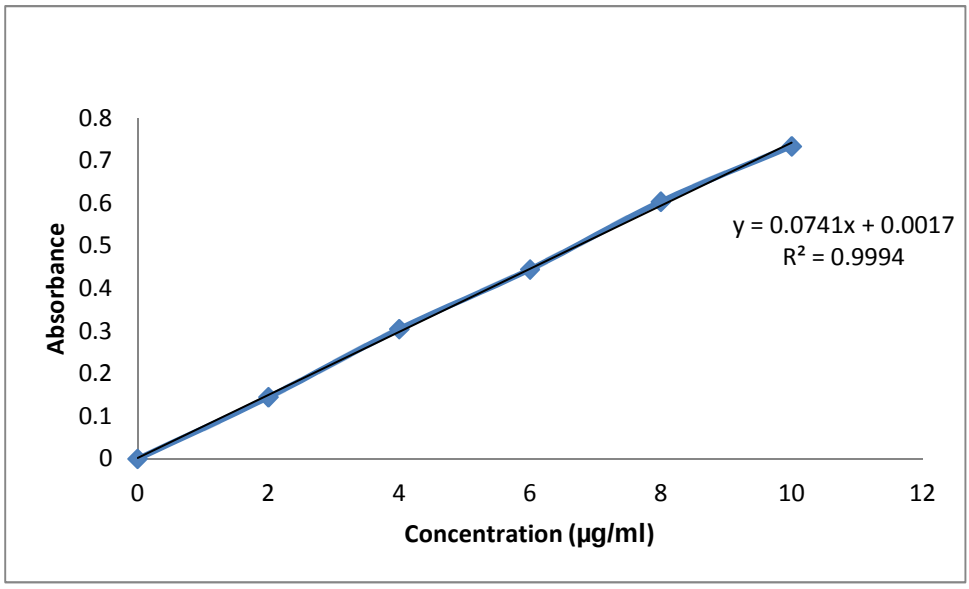


Fig 4: Calibration Curve of Sumatriptan succinate by using pH 6.8 phosphate buffer:

9.1.4.2 Fourier Transform Infra-Red Spectroscopy (FTIR):

The IR spectrum of Sumatriptan succinate is shown in figure 5. The Interpretation of IR frequencies are show in Table 12.

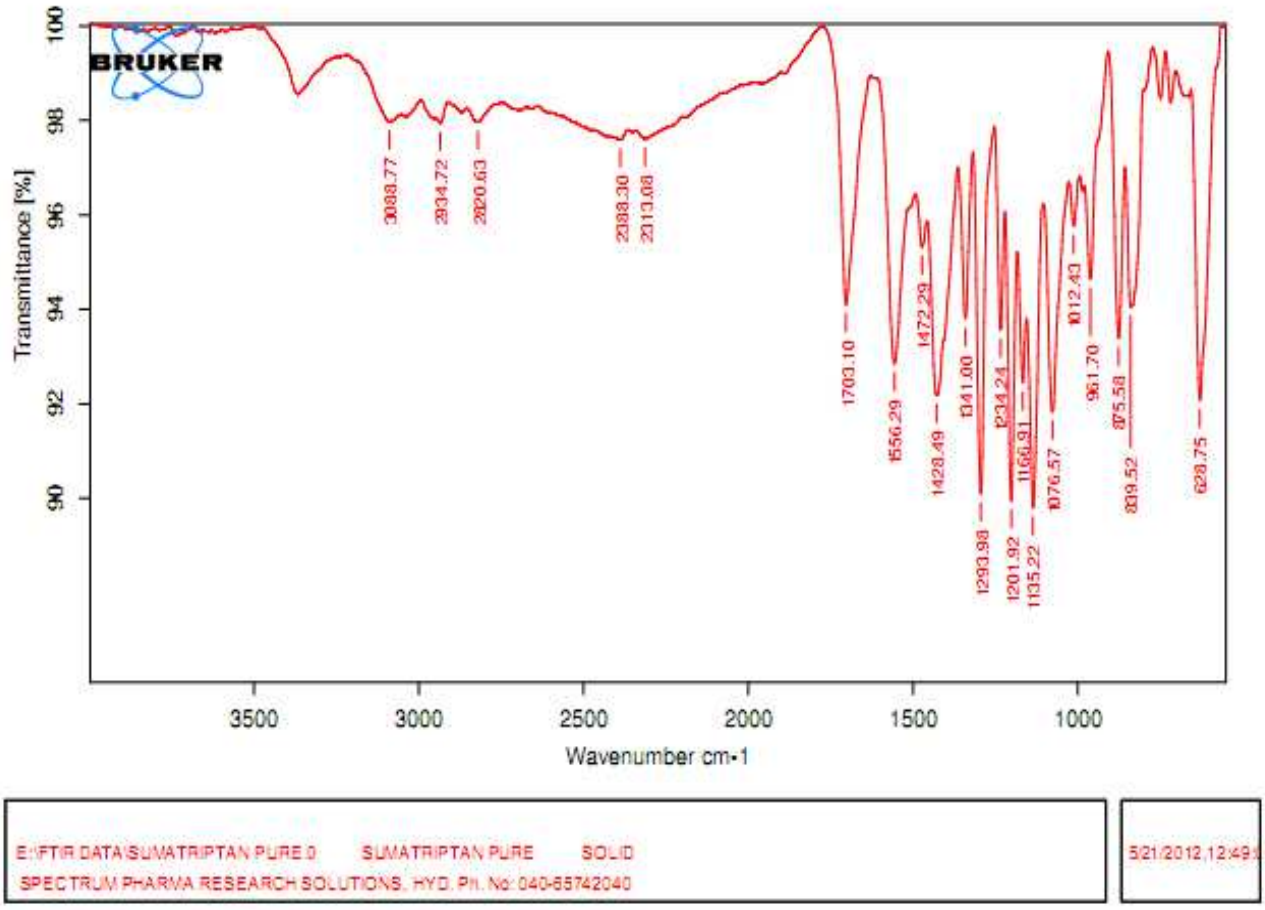


Fig 5: FTIR spectra of Sumatriptan succinate pure drug:

Interpretation of FTIR Spectrum:

Table shows the peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Sumatriptan succinate. Hence, the sample was confirmed as Sumatriptan succinate.

Table 12: Characteristic frequencies in IR Spectrum of Sumatriptan succinate

Functional groups	Wave No. (cm^{-1})
C-H (Aromatic)	3088.77
C=C (Aromatic)	1556.29
C-C (Loop)	1428.49
N-H (Stretching)	3369.75
C-N	1341.00
S=O	1135.22

9.2 DRUG - POLYMERS COMPATIBILITY STUDIES:

9.2.1 Fourier Transform Infra-Red Spectroscopy (FTIR):

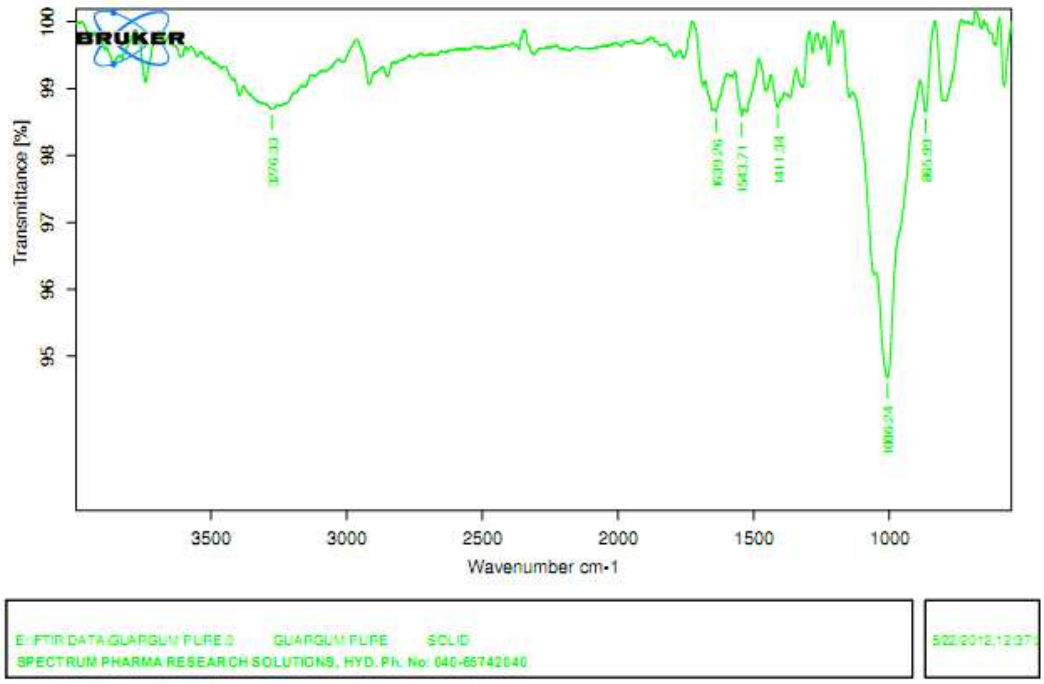


Fig 6: FTIR spectroscopy of guar gum

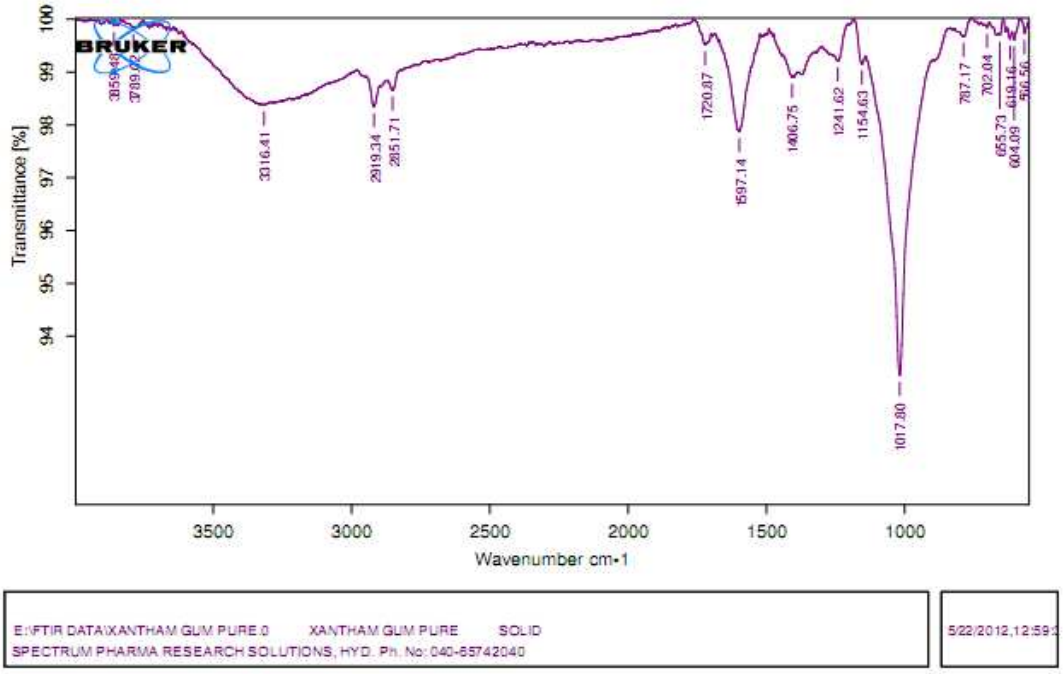


Fig 7: FTIR spectroscopy of xanthan gum

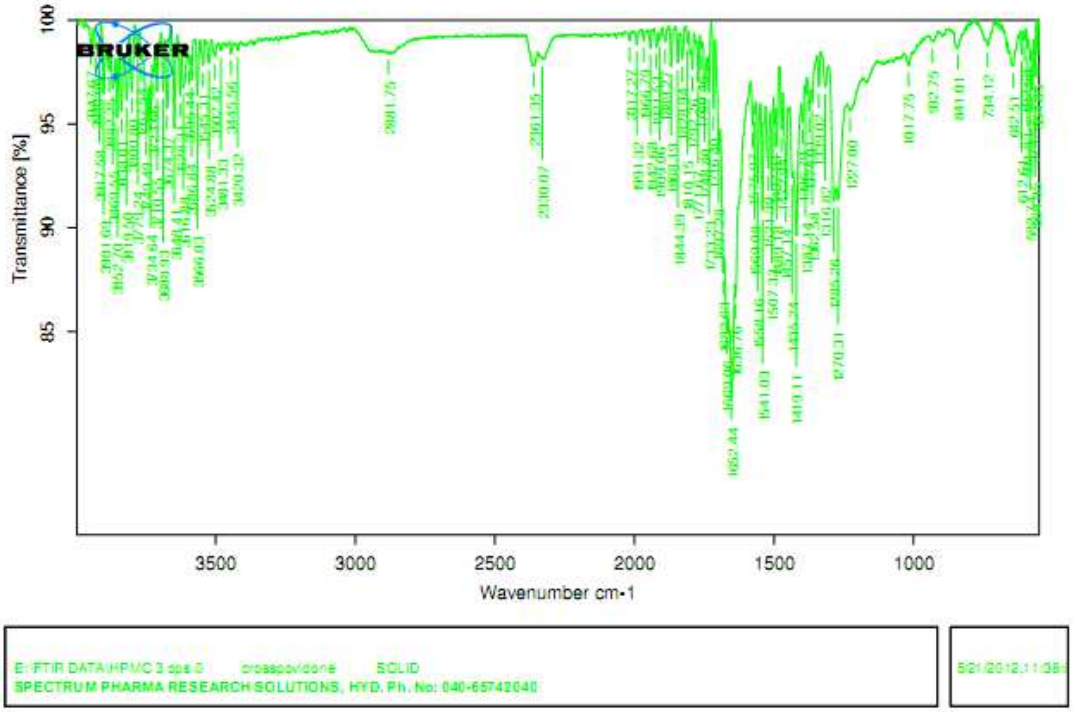


Fig 8: FTIR spectroscopy of crospovidone

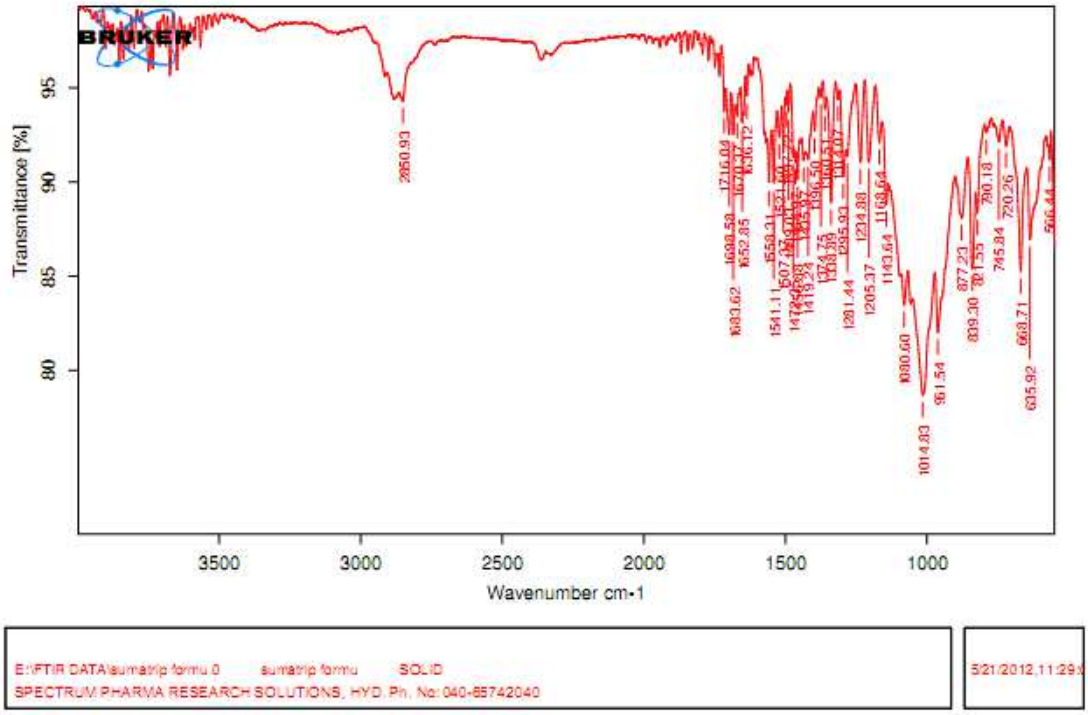


Fig 9: FTIR spectroscopy of best formulation (F7)

Table 13: Characteristic Frequencies in IR Spectrum of Sumatriptan succinate formulation

Functional groups	Wave No. (cm^{-1})
C-H (Aromatic)	2950.93
C=C (Aromatic)	1558.31
C-C (Loop)	1419.24
N-H (Stretching)	3369.75
C-N	1338.89
S=O	1143.64

From the above figure, it can be seen that, the major functional group peaks observed in spectra of Sumatriptan succinate with guar gum, xanthan gum remains unchanged as compared with spectra of sumatriptan succinate. So from the above IR spectra it can be observed that there is no interaction between Sumatriptan succinate and polymers used in the formulations.

9.2.2 Differential Scanning Calorimetry (DSC):

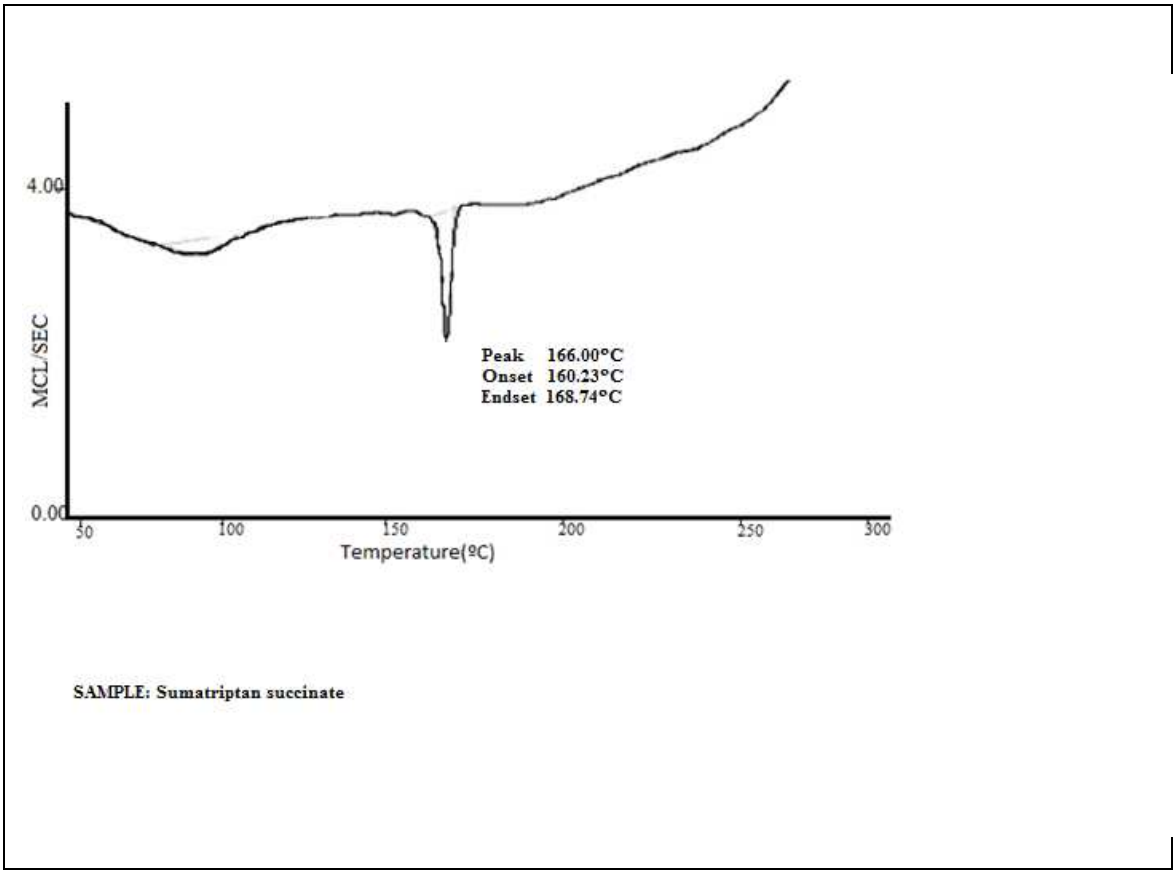


Fig 10: Thermogram of SUMATRIPTAN SUCCINATE

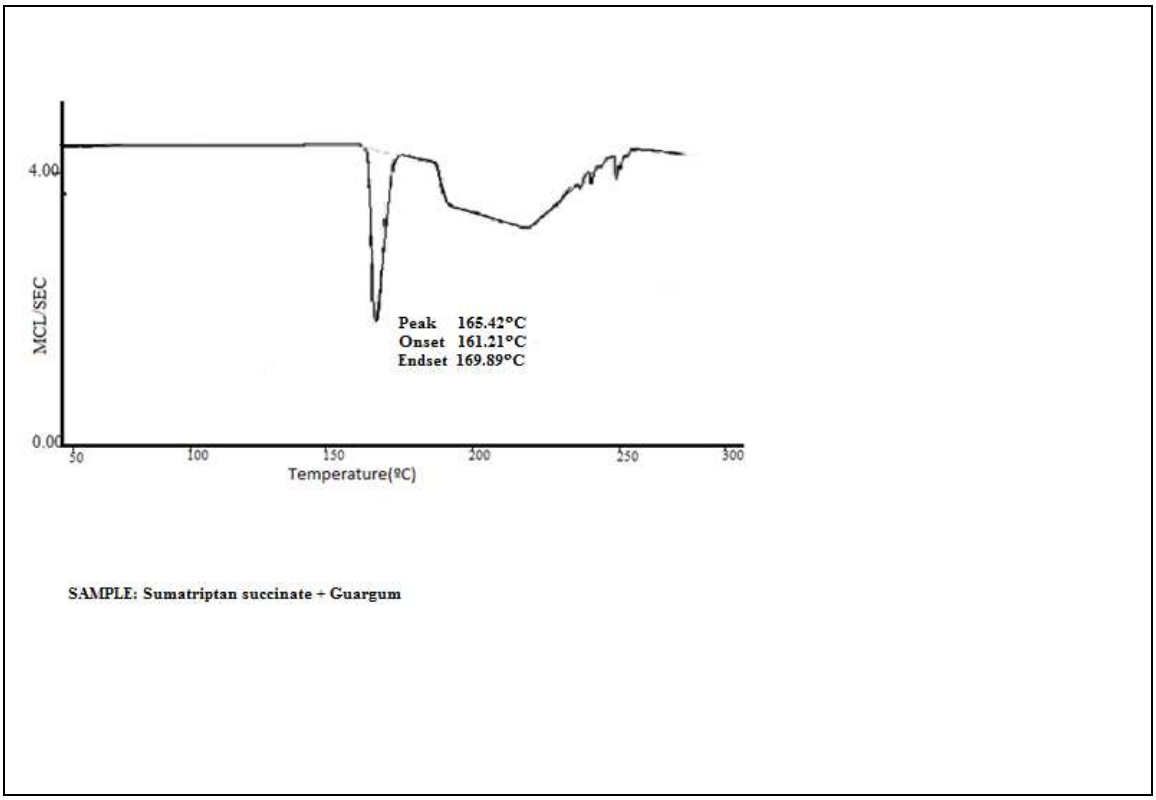


Fig 11: Thermogram of SUMATRIPTAN SUCCINATE + GUAR GUM

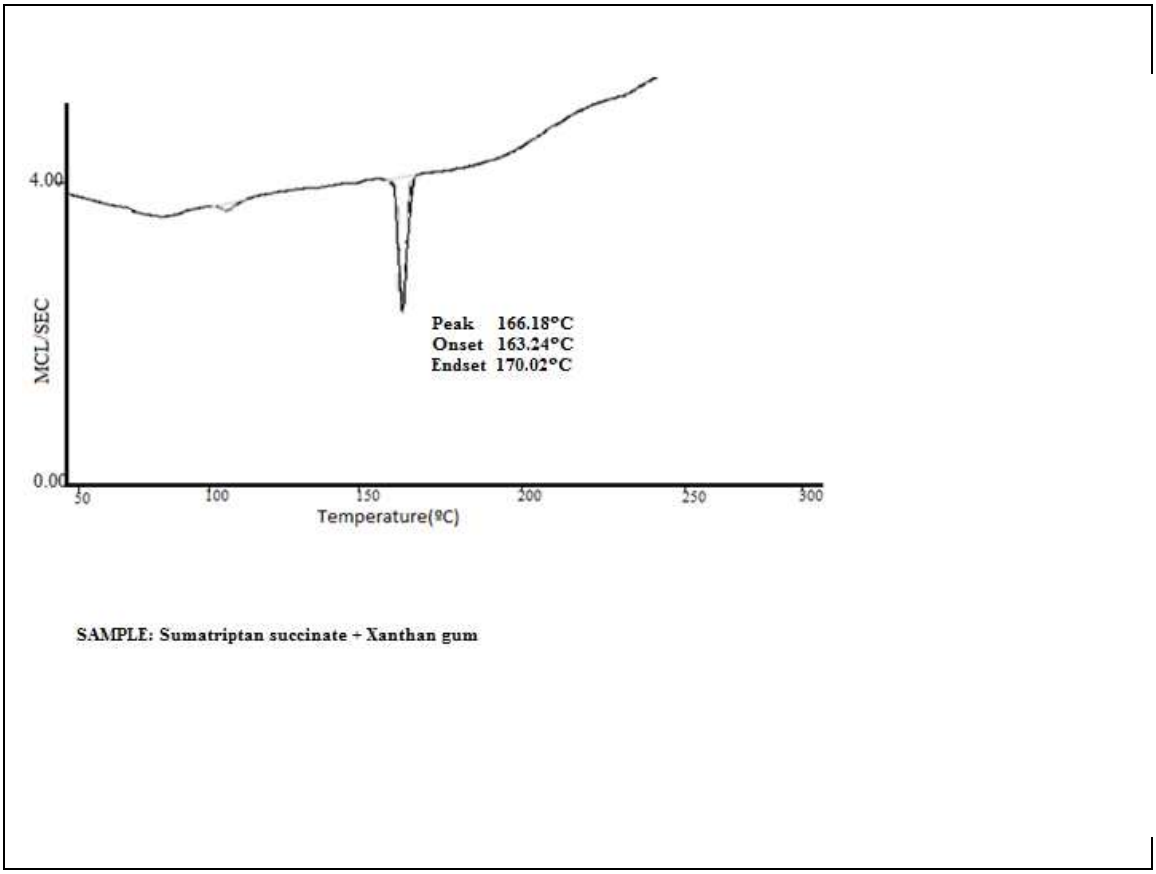


Fig 12: Thermogram of SUMATRIPTAN SUCCINATE + XANTHAN GUM

The results of DSC studies are given in above figure. Pure Sumatriptan succinate showed sharp endotherm at 166°C corresponding to its melting point. There was no appreciable change in the melting endotherms of Sumatriptan succinate with Guar gum and Sumatriptan succinate with Xanthan gum as compared to the thermogram of Sumatriptan succinate. So, it could be concluded that there is no interaction between Sumatriptan succinate and Polymers used in the formulations.

9.3 EVALUATION OF MICROMERITIC PROPERTIES OF POWDER BLENDS:

Table 14: Preformulation parameters of Sumatriptan Succinate SR granules:

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ) (^{0})	Carr's index (%)	Hausner's ratio
F1	0.43±0.007	0.59±0.006	21.45±1.7	17.34±1.7	1.634±1.2
F2	0.41±0.004	0.62±0.009	27.52±0.4	19.54±0.8	1.382±0.7
F3	0.38±0.009	0.53±0.007	34.62±1.5	23.65±1.1	1.442±1.0
F4	0.53±0.005	0.59±0.004	31.43±0.5	21.45±0.9	1.238±1.3
F5	0.45±0.007	0.54±0.005	24.65±1.3	20.61±1.8	1.327±1.3
F6	0.47±0.005	0.58±0.004	27.95±1.4	25.49±1.3	1.643±0.9
F7	0.52±0.008	0.61±0.006	24.27±1.6	19.62±0.9	1.225±0.7
F8	0.49±0.006	0.54±0.003	31.48±0.9	17.50±1.2	1.505±1.2
F9	0.36±0.009	0.58±0.007	26.65±1.0	22.48±1.7	1.605±0.4

All the values are expressed as a mean ± SD., n = 3

Table 15: Preformulation parameters of Sumatriptane Succinate IR layer:

Preformulation parameters	Formulation
Bulk density (gm/ml)	0.42±0.008
Tapped density (gm/ml)	0.54±0.005
Angle of repose (θ)^0	24.11±1.4
Carr's index (%)	22.42±1.8
Hausner's ratio	1.7±1.2

All the values are expressed as a mean ± SD., n = 3

9.3.1 Angle of repose:

The results for angle of repose are recorded in Table 14, 15. Angle of repose ranged from 21.45±1.7 to 34.62±1.5. The flow properties of granules in all formulations exhibit good flow.

9.3.2 Bulk density and Tapped bulk density:

The results are shown in Table 14, 15. The values of BD and TBD were found to be in the range from 0.36±0.009 to 0.53±0.005 gm/cc and 0.53±0.005 to 0.62±0.009 gm/ml respectively. So, it shows that all formulations having good flow properties and packability.

9.3.3 Carr's Compressibility Index:

The results for Carr's Compressibility Index are recorded in Table 14, 15. The Carr's Compressibility Index were in the range from 17.34±1.7 to 25.49±1.3%. This indicates good flow properties of granules.

9.3.4 Hausner's ratio:

The results were summarized in Table 14, 15. The Hausner's ratios were found in the range from 1.225±0.7 to 1.643±0.9. So it indicates good flow properties.

9.4 EVALUATION OF TABLETS:

9.4.1 Evaluation of Physico-chemical properties of tablets

Table 16: Physico-Chemical Properties of Tablets:

Formulation	Wt.variation (%)	Friability* (%)	Hardness** (kg/cm^2)	Thickness** (mm)	Assay* (%)
F1	0.6012	0.25±0.15	5.5±0.7	6.9±0.9	99.49±0.17
F2	0.5988	0.34±0.19	6.0±0.9	6.8±0.2	100.16±0.16
F3	0.6006	0.26±0.17	6.5±0.2	7.0±0.6	99.88±0.25
F4	0.6018	0.12±0.12	9.3±0.7	7.1±0.4	100.5±0.17
F5	0.6005	0.19±0.15	8.6±0.4	6.9±0.2	98.36±0.25
F6	0.5996	0.32±0.13	6.7±0.8	6.8±0.8	98.98±0.16
F7	0.6005	0.28±0.19	6.8±1.2	7.0±0.5	99.60±0.25
F8	0.6008	0.26±0.12	8.4±1.8	6.9±0.6	99.09±0.25
F9	0.6001	0.15±0.16	9.4±0.9	7.2±0.2	100.72±0.19

*****All the values are expressed as a mean ± SD., n = 3

****** All the values are expressed as a mean ± SD., n = 6

9.4.1.1 Appearance:

The tablets were observed visually and did not show any defects such as capping, chipping and lamination after punching.

9.4.1.2 Thickness:

The thickness of formulations ranged from 6.8±0.2 mm to 7.2±0.2mm. The values are recorded in Table 16.

9.4.1.3 Weight Variation:

The percentage deviation from average tablet weight for all the formulations ranged from 499±1.2 to 501±1.5mg. The results are within the specified limits and showed in Table 16. Hence all formulations complied with the test for weight variation as per IP.

9.4.1.4 Hardness:

The results of Hardness of tablets were recorded in Table 16. It was found that the values are ranged from 5.5±0.7 to 9.4±0.9 kg/cm^2. Hardness values were satisfactory and indicated good mechanical strength of tablets.

9.4.1.5 Friability:

The Percentage Friability of all the formulations showed in Table 16. The results are ranged from 0.12±0.12 to 0.34±0.19%. So, the percentage loss of Friability of all the formulations was found to be less than 1 %.

9.4.1.6 Drug content:

Drug content was found to be uniform among different batches of tablets and ranged from 98.4±0.5 to 100.7±0.9%. These results showed that the all formulations having percentage drug content within the specified limits as per USP.

9.4.2 *IN-VITRO* DISSOLUTION STUDIES:

9.4.2.1 *In-vitro* dissolution profile:

Dissolution profile (% drug release) of formulations F1, F2, F3.

Table 17: *In-vitro* dissolution data of Formulation F1, F2, F3

S.No	MEDIUM	TIME(hrs)	Cumulative % drug release of		
			F1	F2	F3
1	0.1N HCl	0	0.00	0.00	0.00
2		0.15	13.1069	10.6103	11.2344
3		0.30	19.2846	19.9724	19.3482
4		0.45	20.7823	21.8448	20.5965
5		1	21.7832	22.3954	22.5879
6		2	23.8459	23.8674	24.7963
7	pH 6.8 phosphate buffer	4	28.8401	29.8935	36.6958
8		6	36.9757	35.7835	43.6383
9		8	43.8476	43.8123	52.5643
10		12	70.4164	66.8263	63.9698
11		24	95.7068	98.6821	96.3459

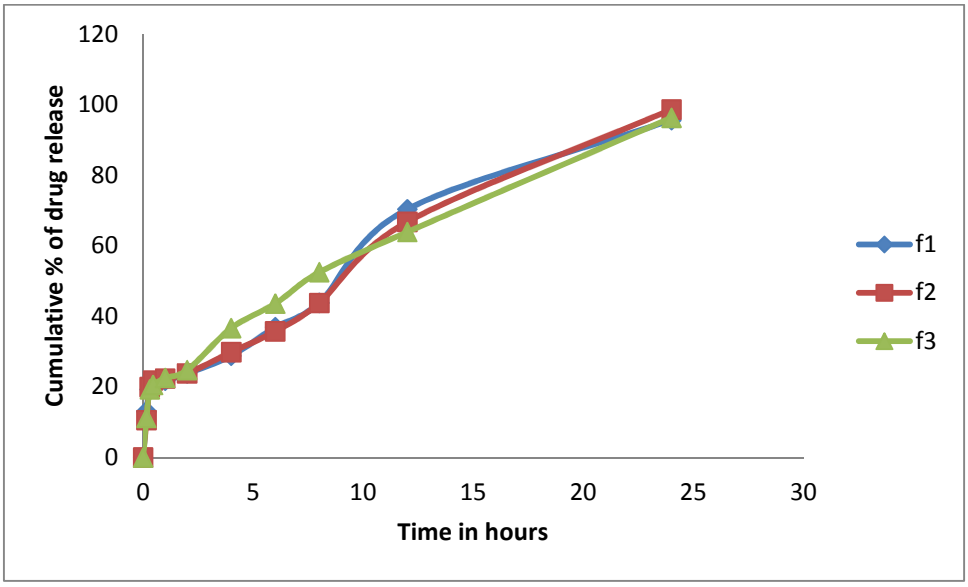


Fig 13: Cumulative percentage drug release profile of F1,F2,F3

Dissolution profile (% drug release) of formulations F4, F5, F6.

Table 18: *In-vitro* dissolution data of Formulation F4, F5, F6

S.No	MEDIUM	TIME(hrs)	Cumulative % drug release of		
			F4	F5	F6
1	0.1N HCl	0	0.00	0.00	0.00
2		0.15	9.3620	11.8586	11.2344
3		0.30	18.7241	19.3482	19.9724
4		0.45	20.0134	20.5965	20.3498
5		1	20.9986	21.8448	22.3994
6		2	23.5893	23.6735	23.9182
7	pH 6.8 phosphate buffer	4	26.8345	34.2164	29.7834
8		6	33.7256	40.1671	37.8203
9		8	39.8345	45.1260	43.8745
10		12	60.8345	58.5150	57.0274
11		24	88.7643	86.7643	84.7972

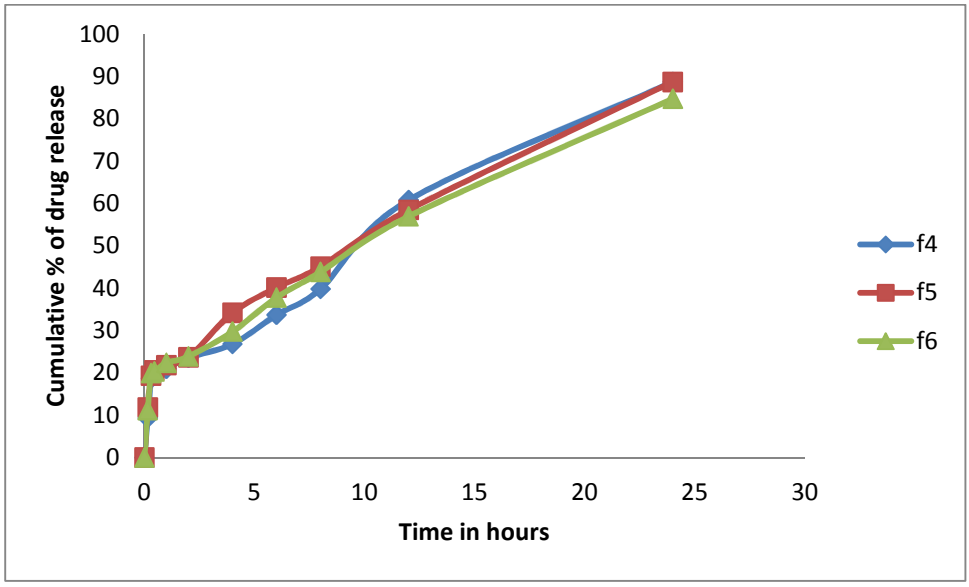


Fig 14: Cumulative percentage drug release profile of F4, F5, F6

Dissolution profile (% drug release) of formulations F7, F8, F9.

Table 19: *In-vitro* dissolution data of Formulation F7, F8, F9

S.No	MEDIUM	TIME(hrs)	Cumulative % drug release of		
			F7	F8	F9
1	0.1N HCl	0	0.00	0.00	0.00
2		0.15	11.8586	12.4827	11.8586
3		0.30	19.3482	18.1	19.9724
4		0.45	20.7459	20.5965	20.8934
5		1	22.6823	21.8934	21.8347
6		2	23.9823	23.8469	24.7823
7	pH 6.8 phosphate buffer	4	28.8456	27.7823	29.7845
8		6	35.8934	34.8349	36.8934
9		8	42.8934	40.8348	44.8736
10		12	65.8349	65.8934	69.7356
11		24	99.4739	94.2191	96.6986

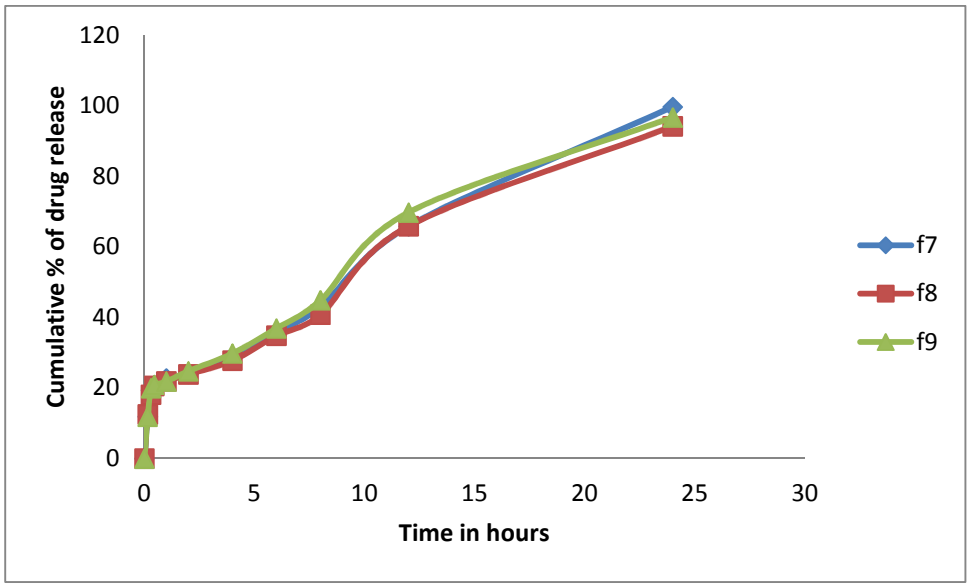


Fig 15: Cumulative percentage drug release profile of F7, F8, F9

In-vitro dissolution studies of all the formulation of Sumatriptan succinate bilayer tablets were carried out in 0.1 N HCl for first two hours and in pH6.8 phosphate buffer for next upto 24 hours. The study was performed for 24 hrs and cumulative drug release was calculated at different time interval**.**

The formulation F1, F2 and F3 showed the drug release 95.7068,98.6821,96.3459 upto 24 hrs but F4, F5 and F6 showed the drug release 88.7643, 86.7643, 84.7972 upto 24 hrs which is having high retarding capacity and due to this the polymer content is decreased in the next three formulations and F7 showed the drug release 99.4739 upto 24hrs and F8,F9 showed the drug release 94.2191, 96.6986% up to 24hours. Hence drug released from F7 formulation shows good retarding capacity and it is considered as the best formulation.

Drug release from all the bilayer tablet formulations followed diffusion control mechanism with R^2 value nearer to one.

9.4.2.2 Kinetics of *In-vitro* Drug Release:

The drug diffusion through most type of polymeric system is often best described by Fickian diffusion (diffusion exponent, n=0.5), but other process in addition to diffusion are important. There is also a relaxation of the polymer chain, which influences the drug release mechanism. This process is described as non- fickian or anomalous diffusion (n=0.5-1.0). Release from initially dry, hydrophilic glassy polymer that swell when added to water and become rubbery, show anomalous diffusion as a result of the rearrangement of macromolecular chain. The thermodynamics state of the polymer and penetrant concentration are responsible for the different type of the diffusion. A third class of diffusion is case-II diffusion (n=1), which is a special case of non- Fickian diffusion. To obtain kinetic parameter of dissolution profile, data were fitted to different kinetic models.

Table 20: Different Kinetic models for Formulations F1-F9

Code	Zero order		First order		Higuchi		Korsemayer's-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	n	
F1	0.9676	0.0166	0.9684	0.0002	0.9742	0.0694	0.9885	0.4032	Peppas
F2	0.9738	0.0164	0.9746	0.0002	0.9778	0.0686	0.9911	0.3970	Peppas
F3	0.9335	0.0162	0.9344	0.0002	0.9745	0.0678	0.9913	0.3775	Peppas
F4	0.9277	0.0136	0.9285	0.0001	0.9681	0.0567	0.9834	0.3596	Peppas
F5	0.9604	0.0137	0.9612	0.0001	0.9719	0.0569	0.9738	0.3475	Peppas
F6	0.9703	0.0138	0.9711	0.0001	0.9722	0.0573	0.9711	0.3482	Matrix
F7	0.9726	0.0169	0.9736	0.0002	0.9602	0.0718	0.9893	0.4051	Peppas
F8	0.9481	0.0293	0.9485	0.0003	0.9911	0.0861	0.9889	0.4462	Matrix
F9	0.8343	0.0296	0.8347	0.0003	0.9882	0.0870	0.9855	0.4476	Matrix

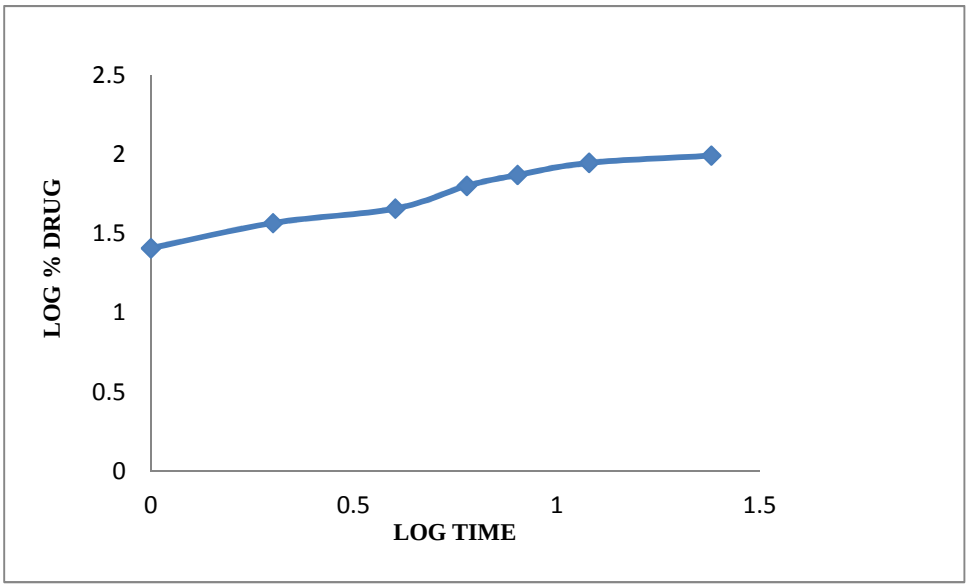


Fig 16: Peppas plot of formulation F1

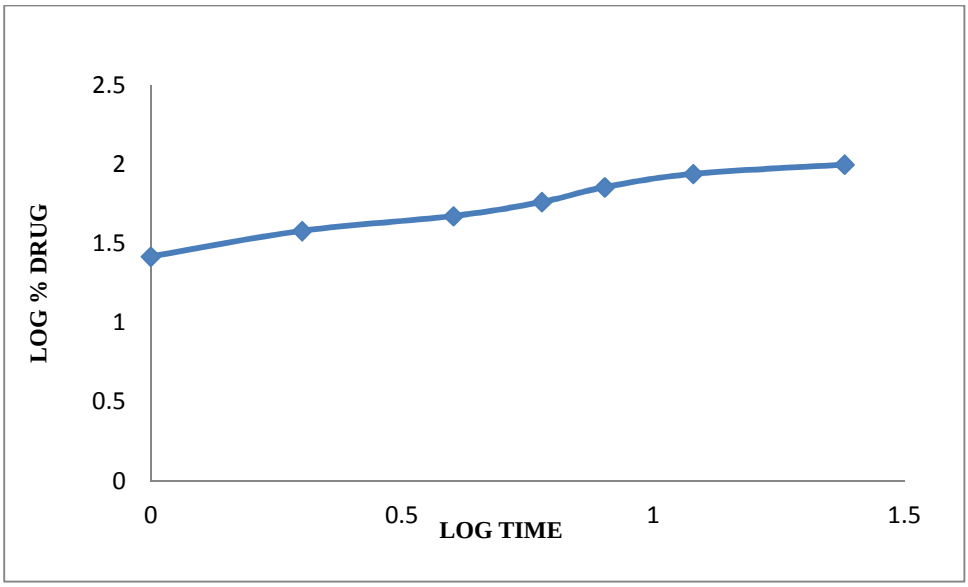


Fig 17: Peppas plot of formulation F2

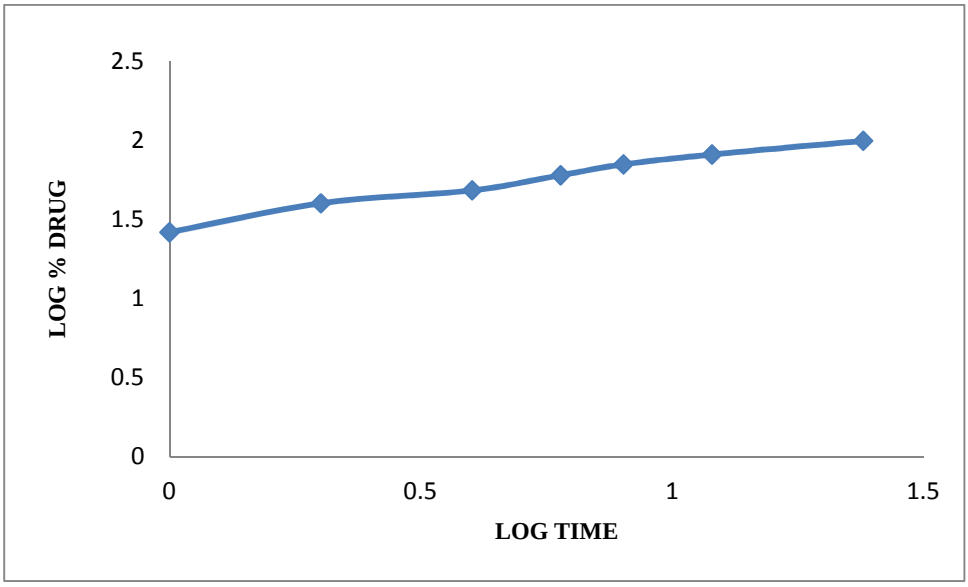


Fig 18: Peppas plot of formulation F3

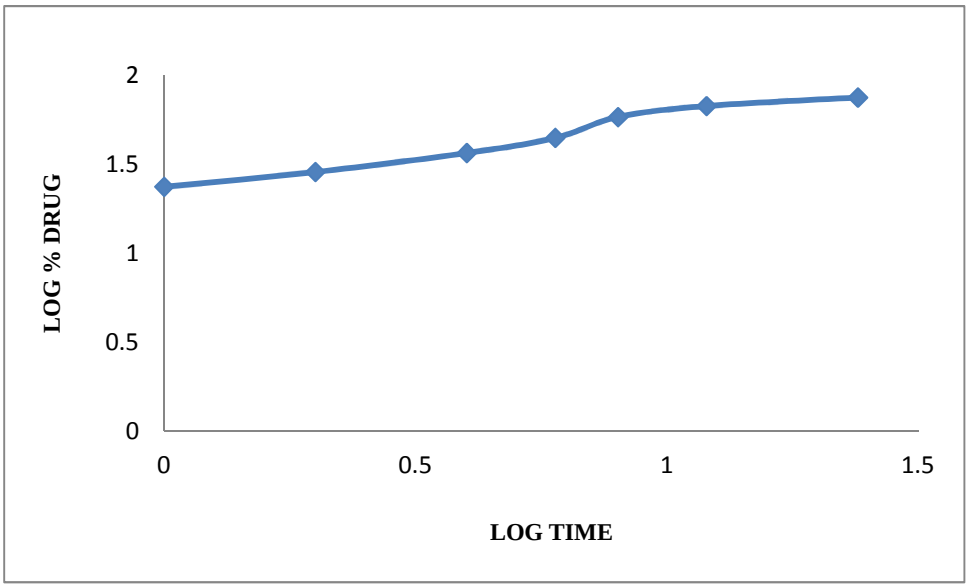


Fig 19: Peppas plot of formulation F4

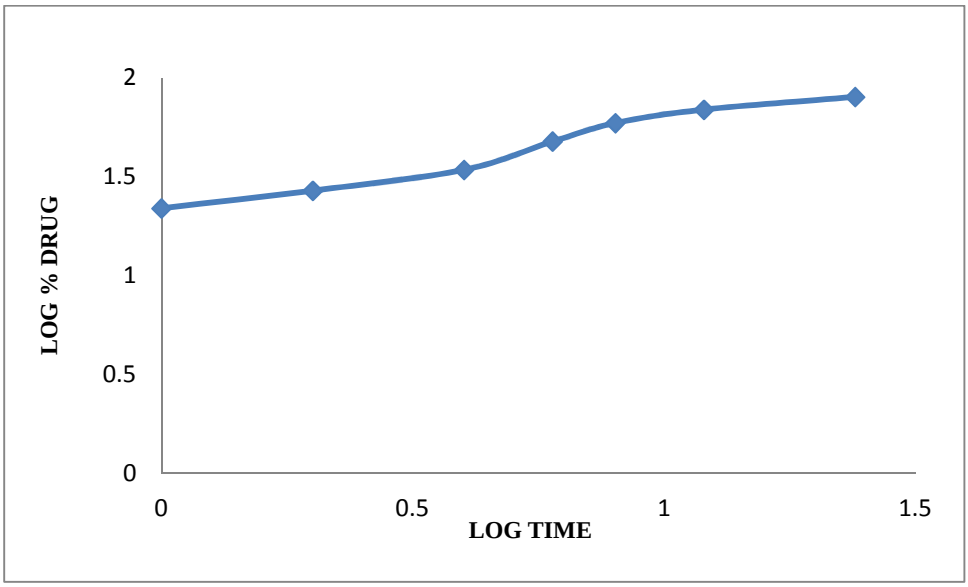


Fig 20: Peppas plot of formulation F5

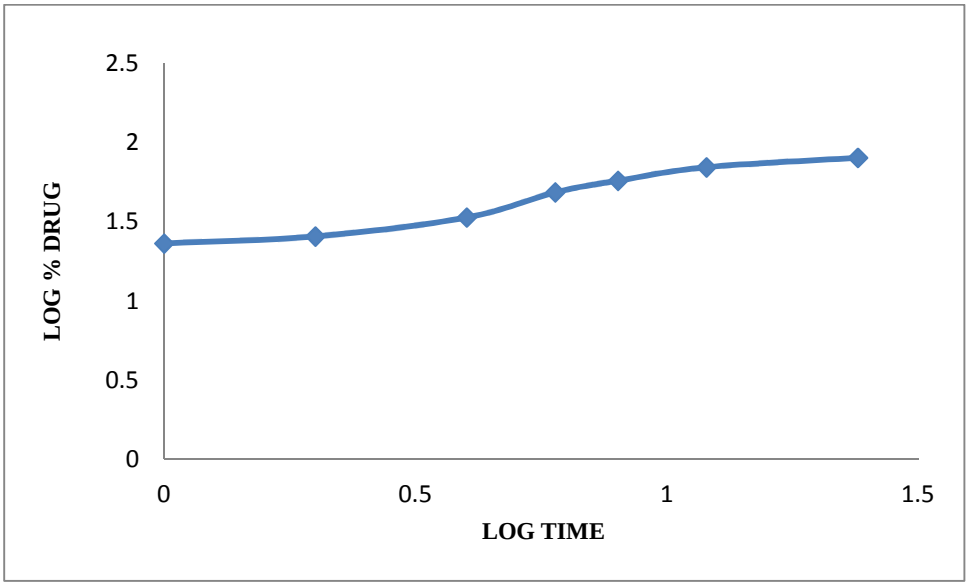


Fig 21: Matrix plot of formulation F6

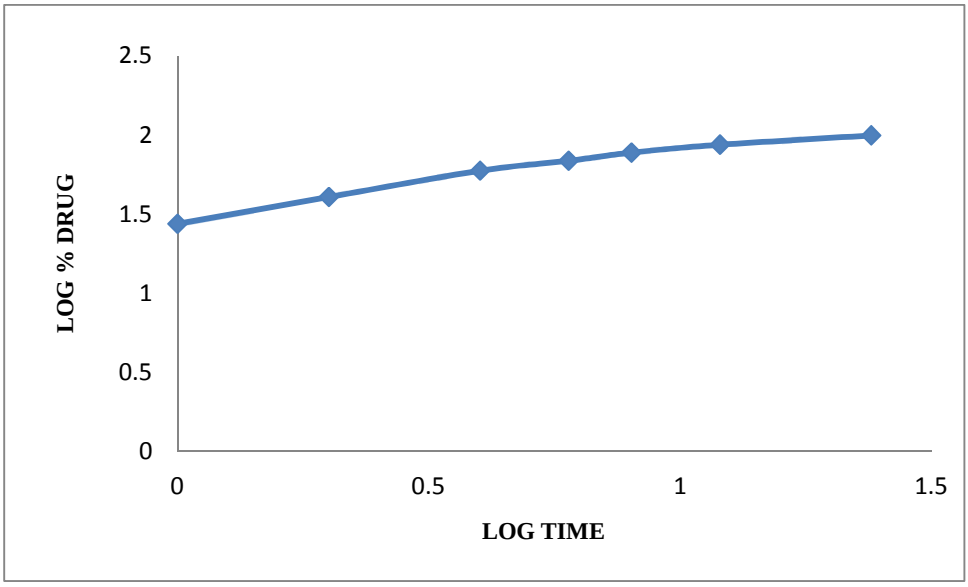


Fig 22: Peppas plot of formulation F7

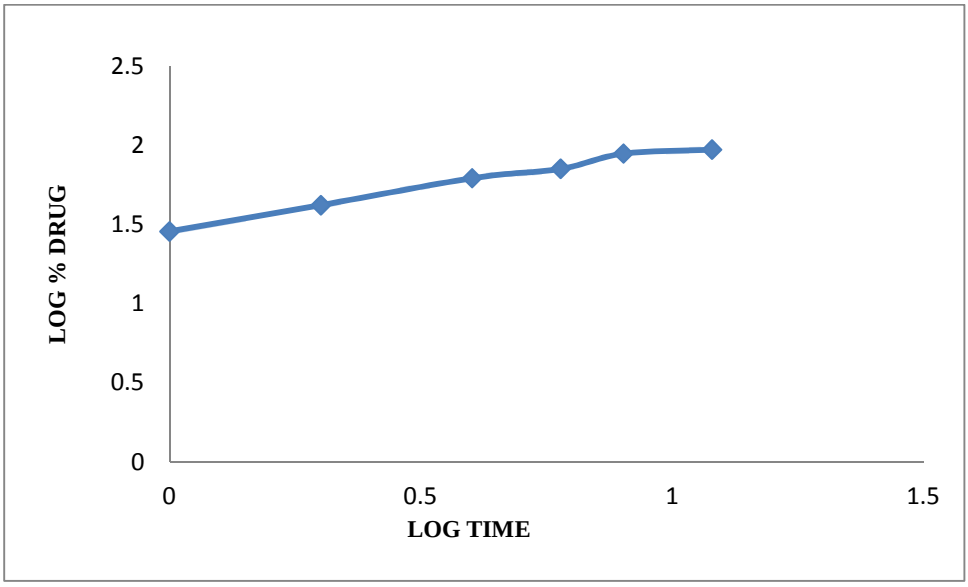


Fig 23: Matrix plot of formulation F8

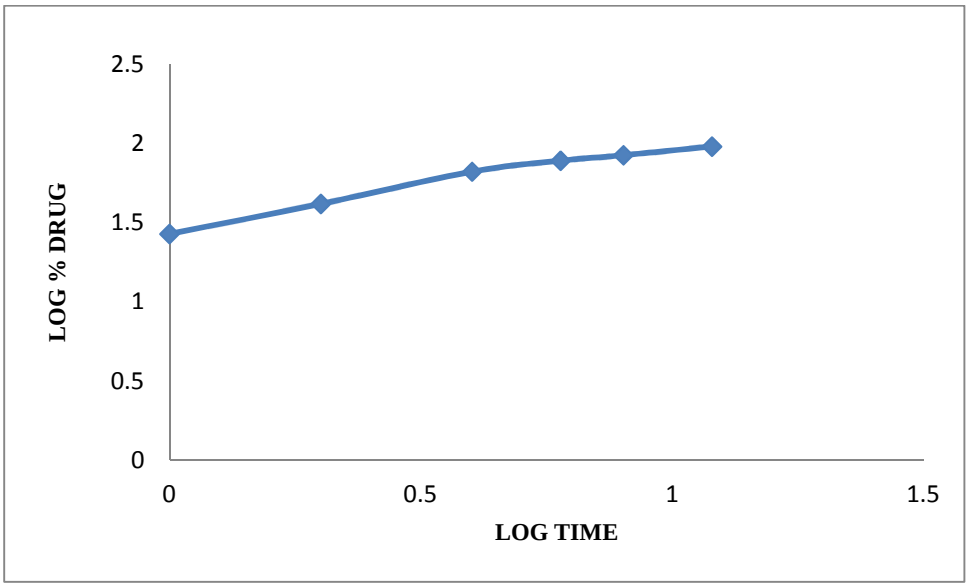


Fig 24: Matrix plot of formulation F9

The data obtained from *invitro* dissolution studies were fitted to zero order, first order, Higuchi, korsmeyers-peppas equation. To confirm the exact mechanism of the drug release korsmeyer and peppas equation superposes two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer.

9.5 STABILITY STUDIES

From the results it was found that formulation F7 is the best formulation amongst the 9 formulations. Thus formulation F7 was selected for stability studies.

9.5.1 Stability studies at the end of First month (30 days):

9.5.1.1 Hardness:

The hardness of tablet after one month of stability studies was studied. The results are within the limits. The data is shown in Table 21.

Table 21: Hardness of formulation F1 at the end of 1 month of stability

S. No.	Formulation	Hardness (kg/cm^2)
1.	F7	6.7±1.6

All the values are expressed as a mean ± SD., n = 6

9.5.1.2 Drug Content :

The Percentage drug content of tablet after one month of stability studies was studied. The results are within the official limits. The data is shown in Table 22.

Table 22: Drug content of formulation F7 at the end of 1 month of stability

S. No.	Formulation	Percentage drug content
1.	F7	99.20 ±1.4

All the values are expressed as a mean ± SD., n = 3

9.5.1.3 *In-vitro* dissolution study:

The Cumulative percentage drug release from F7 tablet after one month of stability was studied. The data is shown in Table 23.

Table 23: *In-vitro* dissolution data of formulation F7 at the end of 1 month of stability

S.No	TIME(hrs)	Cumulative % drug release of F7
1	0.15	11.7210
2	0.30	18.7254
3	0.45	20.26514
4	1	22.3561
5	2	23.0689
6	4	27.1805
7	6	34.0239
8	8	42.1269
9	12	65.0376
10	24	99.0526

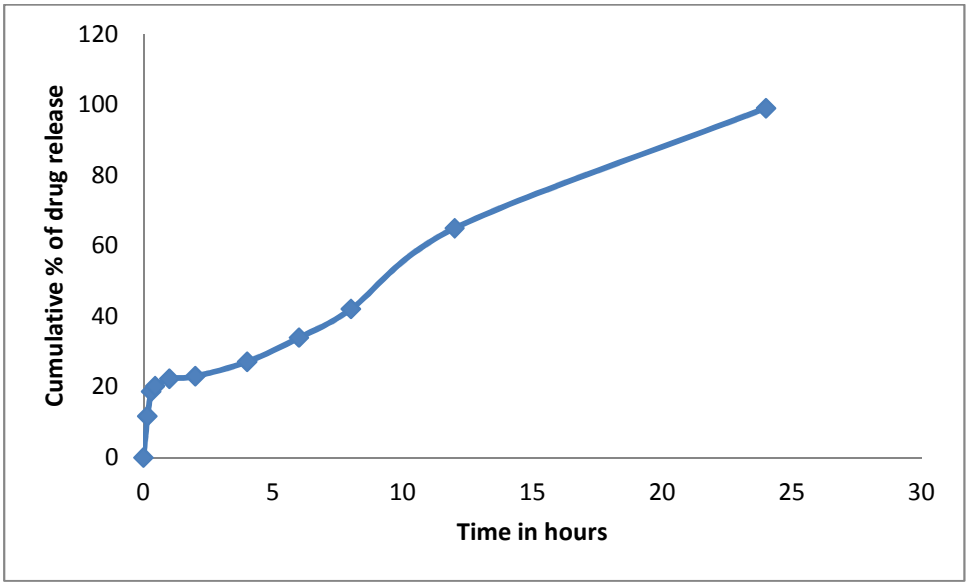


Fig 25: *In-vitro* dissolution profile of formulation F7 at the end of 1 month of stability

9.5.2 Stability studies at the end of Second month (60 days):

9.5.2.1 Hardness:

The hardness of tablet after Two months of stability studies was studied. The results are within the limits. The data is shown in Table 24.

Table 24: Hardness of formulation F7 at the end of 2 months of stability

S. No.	Formulation	Hardness (kg/cm^2)
1.	F7	6.7±0.3

All the values are expressed as a mean ± SD., n = 6

9.5.2.2 Drug content:

The Percentage drug content of tablet after Two months of stability studies was studied. The results are within the official limits. The data is shown in Table 25.

Table 25: Drug content of formulation F7 at the end of 2 months of stability

S. No.	Formulation	Percentage drug content
1.	F1	99.08 ±0.60

All the values are expressed as a mean ± SD., n = 3

9.5.2.3 *In-vitro* dissolution study:

The Cumulative Percentage Drug Release from F7 tablet after Two months of stability was studied. The data is shown in Table 26.

Table 26: *In-vitro* dissolution data of formulation F7 at the end of 2 months of stability

S.No	TIME(hrs)	Cumulative % drug release of F7
1	0.15	10.8934
2	0.30	18.0657
3	0.45	19.8624
4	1	22.0364
5	2	22.9248
6	4	26.8649
7	6	33.9214
8	8	41.8624
9	12	64.7964
10	24	98.3269

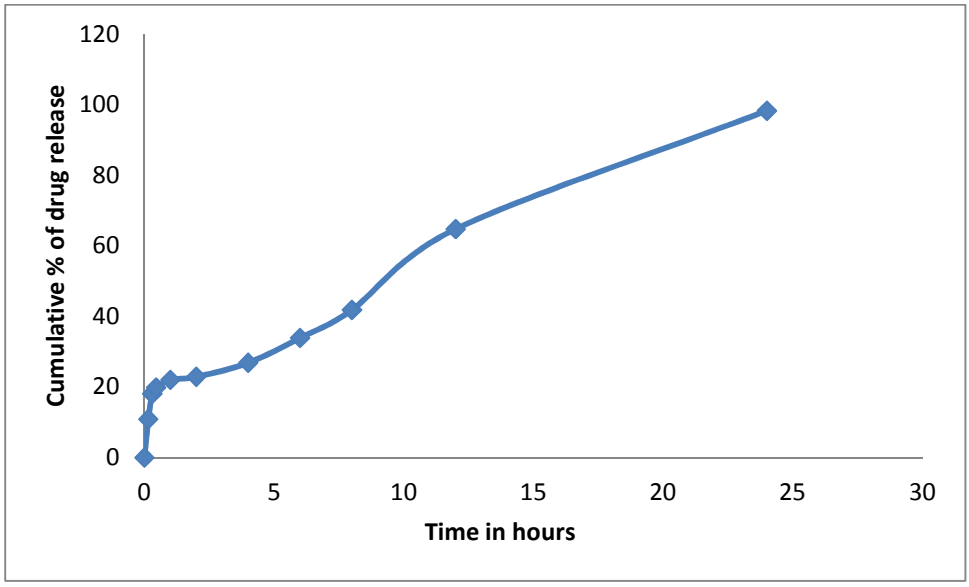


Fig 26: *In-vitro* dissolution profile of formulation F7 at the end of 2 months of stability

9.5.3 Stability studies at the end of Third month (90 days):

9.5.3.1 Hardness:

The hardness of tablet after Third months of stability studies was studied. The results are within the limits. The data is shown in Table 27.

Table 27: Hardness of formulation F7 at the end of 3 months of stability

S. No.	Formulation	Hardness (kg/cm^2)
1.	F7	6.6±1.1

All the values are expressed as a mean ± SD., n = 6

9.5.3.2 Drug content:

The Percentage drug content of tablet after Third month of stability studies was studied. The results are within the official limits. The data is shown in Table 28.

Table 28: Drug content of formulation F7 at the end of 3 months of stability

S. No.	Formulation	Percentage drug content
1.	F7	98.7±0.8

All the values are expressed as a mean ± SD., n = 3

9.5.3.3 *In-vitro* dissolution study:

The Cumulative percentage drug release from F7 tablet after Three months of stability was studied. The data is shown in Table 29.

Table 29: *In-vitro* dissolution data of formulation F7 at the end of 3 months of stability

S. No	TIME(hrs)	Cumulative % drug release of F7
1	0.15	10.2648
2	0.30	17.9561
3	0.45	19.1359
4	1	21.9624
5	2	22.3219
6	4	26.0364
7	6	33.0934
8	8	40.9632
9	12	64.0329
10	24	98.1298

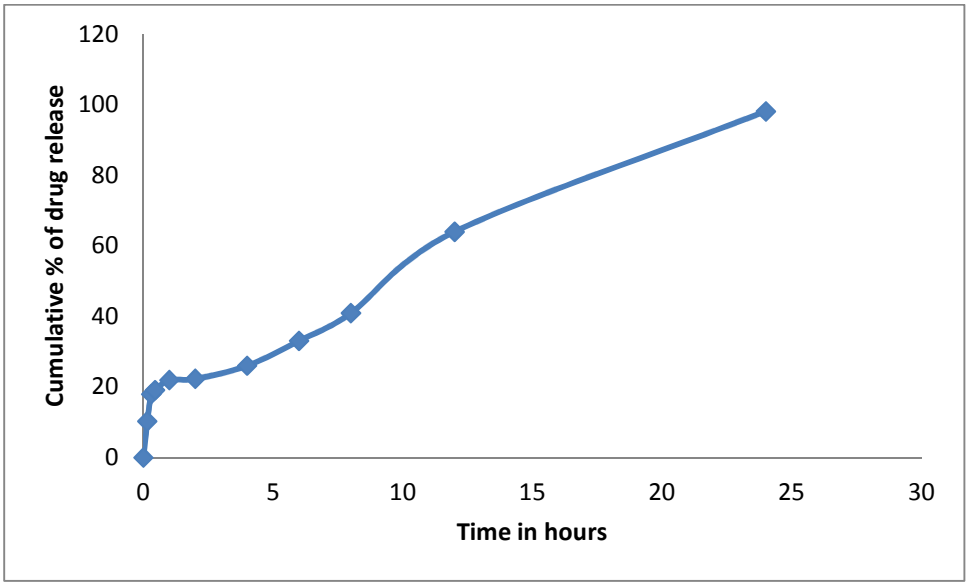


Fig 27: *In-vitro* dissolution profile of formulation F7 at the end of 3 months of stability

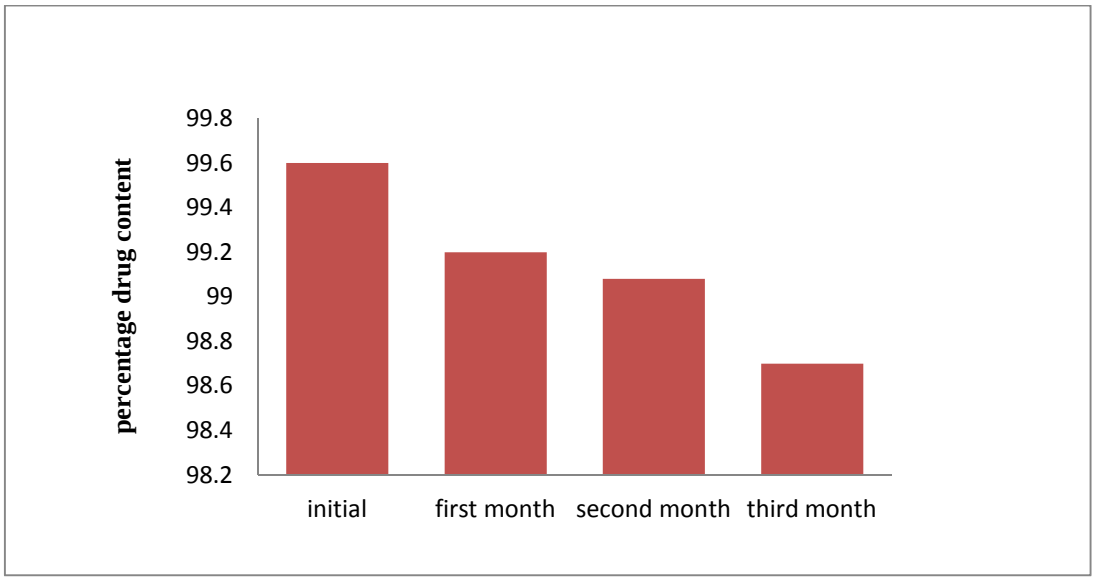


Fig 28: Comparison of drug content for formulation F7 with initial and different periods of stability

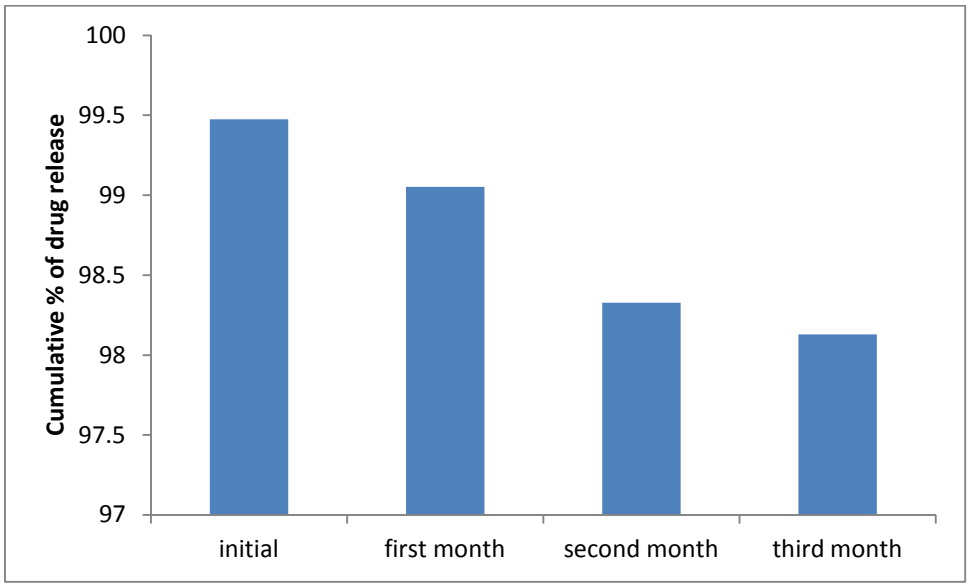


Fig.29 Comparison of cumulative percentage drug released at the end of 24 hours for formulation F7 with initial and different periods of stability

No statistically significant differences were observed in Hardness, percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies.

So it can be concluded that the formulation F7 is stable for short term storage conditions.

CHAPTER-10

SUMMARY AND CONCLUSIO

10. SUMMARY AND CONCLUSIONS

The formulation development and *in-vitro* evaluation of bilayer drug delivery system of Sumatriptan succinate tablets was performed in the present study.

The bilayer tablets of sumatriptan succinate were prepared by using polymers like guar gum, xanthan gum, sodium alginate for the treatment of migraine. The dissolution study of F7 bilayer tablets containing guar gum and xanthan gum was concluded the best formulation among other formulations, which showing the most desired drug release. It will be considered as optimized formulation.

The optimized formulation F7 was subjected for stability studies, the formulation was found to be stable in short term stability study.

Preformulation study was carried out for powder blends, it was evaluated to determine the flow characteristics by angle of repose, bulk density, tapped density, carr's index and Hausner's ratio. The data obtained from these studies indicated that the powder blends had good flow properties.

The tablets were prepared with different ratios of polymers by direct compression and wet granulation technique. The formulated tablets were evaluated for physical characterization like thickness, hardness, friability, weight variation and drug content. All the physical parameters of prepared tablets comply with IP specifications.

Evaluation studies of all formulations showed that the drug content, weight variation and friability as per the standards given in IP. The hardness of all formulations was within the limits.

The *in-vitro* dissolution studies closely indicate that among nine formulations the formulation F7 was found to be the best with good retard of drug release.

The regression correlation co-efficient value was concluded in kinetics modeling of drug dissolution profile for all formulations. The formulation F7 having R^2 value lies between 0.5 to 1.0. Hence it is concluded that formulation F7 following peppas drug release.

From the stability data, it can be concluded that there was no significant changes in any parameters. Hence the formulation F7 is considered to be highly stable formulation.

The overall studies indicate that polymers Xanthan gum, Guar gum showed satisfactory properties. Among the nine formulations the formulation F7 exhibited optimum drugs release profile. Hence, it is concluded that the formulation F7 will be useful for bilayer drug release.

CHAPTER-11

FUTURE PROSPECTUS

11. FUTURE PROSPECTS

In the present work bilayer tablets of Sumatriptan succinate were formulated using natural polymers by direct compression and wet granulation methods. In this work only physicochemical characterization, formulation and *in-vitro* evaluation of bilayer tablets of Sumatriptan succinate was done. Along with *in-vitro* release study *in-vivo* release behaviour of drug is also important. So in future *in-vivo* release study using different models are required to set the *in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.

.

CHAPTER-12

BIBLIOGRAPHY

12. BIBLIOGRAPHY

1) Anonymous. Indian Pharmacopoeia. Published by the Controller of Publication, Govt. of India, Ministry of Health and Family Welfare, New Delhi, I and II, 179-183, 662-663, **2007**.
2) Anonymous. United State Pharmacopoeia. The United States Pharmacopoeial convention Inc, Rockville, MD, USA, 1988-1989, **2007**.
3) Anonymous. http://www.wikipedia.com/sumatriptan succinate.
4) Aulton M. Pharmaceutics: The Science of Dosage Form Design, International Student Edition, Newyork, 168-179, 304-321, 347-668, **2007**.
5) Banker G and Rhodes C. Drug and Pharmaceutical Sciences, Modern Pharmaceutics, 3rd edition, 72, 333-394.
6) Bhalala chirag, Chauhan Sachin, Balaraman R, Seth A. K., Shah Chainesh, Dhamat Khushal and Hitesh Gevariya. Formulation and evaluation of sustained release bilayer tablets of Metformin HCl and Pioglitazone HCl, *World Journal of Pharmaceutical research.*1(2), 242 257, **2012**.
7) Bentley's. Text book of Pharmaceutics, 8th edition, pg.no.140.
8) Bogner RH. Bioavailabilty and Bioequivalence of extended release oral dosage forms, US pharmacist, 22, 3-12, **1997**.
9) Brahmankar D.M. and Jaiswal S.B. Biopharmaceutics and pharmacokinetics: A Tretise, 1st edition, Vallabh prakashan, New delhi, 335-337, 2006.
10) Chien YW. Novel drug delivery system, Informa healthcare, 2nd edition revised and expanded, 50, 139-140, **2010**.
11) Chinam Niranjan Patra, Arethi Bharani Kumar, Hemant Kumar Pandit, Satya Prakash Singh and Meduri Vimala devi. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride, Acta Pharm, 479–489, **2007**.
12) Chitra Karthikeyini.S, S. Jayaprakash, A.Abirami and S.Mohamed Halith. Formulation and evaluation of Aceclofenac sodium bilayer sustained release tablets, *Int. J. ChemTech Res*, 1(4), 1381-1385, **2009**.
13) Cremer K. Pharmaceutical application of layer tablet, *AAPS PharmaSciTech*, 1, 1-10, **2001**.
14) Darshana HD, Mangal NS and Sudhakar GD. Design and evaluation of an extended release tables of prochlorperazine maleate, Indian Drugs, 38, 69-74, **2000**.

15) Dhruvita Patel, Ankita Patel and Trupti Solanki. Formulation and evaluation of bilayer tablet by using melt granulation technique for treatment of Diabetes mellitus, *J Pharm Bioall Sci*, 4, 37-39, **2012**.

16) D.K. Arulmozhi, A. Veeranjaneyulu and S.L. Bodhankar. Migraine: Current concepts and emerging therapies, Vascular Pharmacology, 43, 176-187, **2005**.

17) Dr P.K. Sahoo. Pharmaceutical Technology. Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, 2-3.

18) Edvinsson, L. Blockade of CGRP receptors in the intracranial vasculature: a new target in the treatment of migraine, Cephalalgia, 24, 611 –622, **2004**.

19) Fassihi R, Yang L, Venkatesh G. Compaction simulator study of a novel triple layer tablet matrix for industrial tableting, *Int. J. Pharma*,152,45-52, **1997**.

20) Girish S. Sonar, Devendra K. Jain and Dhananjay M. More. Preparation and *in vitro* evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate, *Asian Journal of Pharmaceutical Sciences*, 2 (4), 161-169, **2007**.

21) Goldstein, D.J. Offen, W.W. Klein, E.G. Phebus and L.A. Lanepitant, an NK-1 antagonist, in migraine, Cephalalgia, 19, 377, **1999**.

22) Goodman and Gilman. The pharmacological basis of therapeutics, 10th edition, Edited by Joel G. Hardman and Lee E. Limbird, McGraw-Hill Medical publishing Division, 278-281.

23) G.Vinoth Kumar, K.Anand babu and C.Ramasamy. Formulation and Evaluation of Bilayered Tablets of Cefixime trihydrate and Dicloxacillin sodium, *Int. J. PharmTech Res*, 3(2), 613-618, **2011**.

24) Hosna Banu, Mostafa Reaj Sahariar, Muhammad Shahdaat Bin Sayeed, Irin Dewan and S.M. Ashraful Islam. Formulation development of bi-layer acetaminophen tablets for extended drug release, *J. Chem. Pharm. Res*, 3(6), 348-360, **2011**.

25) Jain Jitendra, Bhavna H. marya, Mittal R Patani and Mandev patel. Formulation and Evaluation of Indomethacin Bilayer Sustained Release Tablets, *Int.J. PharmTech Res*, 3(2), 1132-1138, **2011**.

26) Jain N. K. Progress in Controlled and Novel Drug delivery systems, 1st edition, C. B. S. publishers, New Delhi, 76-97, **2008**.

27) Janes T. Garnsten and Rhodes C. T. Drug stability principles and practice, 3rd edition, Mercel Dekker Inc, New York, 414-481, **2000**.

28) Kiran muscle, S.A Payghan and Dr. J.I.Disuza. Formulation, Evaluation and development of bilayer tablet, *IJPRD*, 3(10), 80-87, **2011**.

29) Lachman L, Liberman H. and Kanig J. The Theory and practice of Industrial Pharmacy, 3rd edition, 293-345,346-373.

30) Larry L. Augsburger and Stephen W. Hoag. Pharmaceutical dosage forms:Tablets, 2, 173-79.

31) Li B, Zhu J, Zheng C and Gong W. Novel system for three-pulse drug release based on tablet in capsule devices, *Int J. Pharma*, 352, 159-164, **2007**.

32) Lieberman HA, Lieberman L and Schwartz B. Pharmaceutical dosage form: Tablets, CBS publishers and Distributors, 2nd edition revised and expanded, 1, 179-181,225-239, 274-275, **2008**.

33) Loyd V. Allen, Nicholas G. Popovich and Howard C. Ansel. Ansel's pharmaceutical dosage form and drug delivery system, 8th edition, 209.

34) MA Naeem, A Mahmood, SA Khan and Z Shahiq. Development and evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen, *Tropical Journal of Pharmaceutical Research*, 9 (4), 347-354, **2010**.

35) Metkar Vishal, Kumar Anuj, Pant Pankaj, Pal Deepti1, Sahu Shraddha, Shurngarpure Mansee and Madhusudan Dutta. Formulation development and evaluation of Bilayer tablets of Lornoxicam, *Int. J. Drug Dev. & Res*, 4 (2), 173-179, **2012**.

36) Modi Foram P and Patel Priyal R. Formulation, Optimization & Evaluation of Fixed Dose Combination Moisture Barrier Film Coated Bilayer Tablet of Artesunate & Amodiaquine Hydrochloride, *Int. J. PharmTech Res*, 3(4), 2124-2134, **2011**.

37) Mr. Ashish A Pahade, Dr. Mrs. V.M.Jadhav and Dr. Mr. V.J.Kadam. Formulation and development of a bilayer sustained released tablets of Isosorbide mononitrate, *Int J of Pharma and Bio Sciences*, 1(4), 305-314, **2010**.

38) Narasaiah VL, Saravanan G, Kumar MR, Reddy BK, Srikanth P, Kumar MS, Satyanand S and Ashok A. Formulation, charecterisation and *in vitro* evaluation of sumatriptan succinate floating tablets, *JITPS*, 1(5), 191-203, **2010**.

39) Neil IM (Eds). The Merck Index- An Encyclopedia of chemicals, Drugs and Biologicals, 14th edition, NJ (USA), Merck Research Laboratories,8996, **2001**.

40) Ohmori S and Makino T. Sustained release phenylpropanolamine hydrochloride bilayer tablets containing HPMC2208 matrix, Formulation and dissolution characteristics, *Chem Pharma. Bull***,** 48(5),673-677, **2000**.

41) Patra CN, Arethi BK, Pandit HK and Singh SP. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride, *Acta pharma*, 57, 479-489, **2007**.

42) Peterson, K.A, Nilsson, E, Olesen, J and Edvinsson, L. Presence and function of the calcitonin gene-related peptide receptor on rat pial arteries investigated *in vitro* and *in vivo.* Cephalalgia, 25, 424–432, **2005**.

43) Preeti Karwa and P. V. Kasture. Formulation and *in vitro* evaluation of Bilayer Tablets of Zolpidem tartrate for Biphasic Drug Release, *Int. J. PharmTech Res*, 3(4), 1919-1929, **2011**.

44) Rawlins EA. Bentley's text book of pharmaceutics, 8th ed. London, Bailliere Tindall, **1992**.

45) Raymond CR, Paul JS and Sian C Owen's. Handbook of Pharmaceutical Excipients, Published by the Pharmaceutical Press 5th edition.

46) Remya P.N, Damodharan N and Sulakshan Kumar C.V. Formulation and Evaluation of Bilayered Tablets of Ibuprofen and Methocarbamol, *Int. J. PharmTech Res*, 2(2), 1250-1255, **2010**.

47) R.Natarajan, Nimesh Patel and N.N.Rajendran. Formulation and Evaluation of Immediate release Bilayer Tablets of Telmisartan and Hydrochlorothiazide, *Int J of ayurvedic & herbal medicine*, 1(1), 1-5, **2011**.

48) Robert M. Silverstein and Fransis S. Webster. Spectrometric identification of organic compounds. 6th edition, John Wiley & Sons Inc, US, 71-144, **2003**.

49) R. T. Jadhav, Payal H. Patil and Pratibha R. Patil**.** Formulation and evaluation of bilayered tablet of Piracetam and Vinpocetine, *J. Chem. Pharm. Res*, 3(3), 423-431, **2011**.

50) Sharmin Rahman, Md. Abdullah Al Masum, Florida Sharmin, S. M. Ashraful Islam and Md. Selim Reza. Formulation and Evaluation of Bi-layered Sustained Release Matrix Tablets of Tramadol Hydrochloride, *Journal of Applied Pharmaceutical Science*, 2(6), 129-134, **2012**.

51) Shidhaye SS, Saindane NS, Sutar S and Kadam V. Mucoadhesive bilayered patches for administration of sumatriptan succinate, *AAPS Pharma Sci Tech*, 9(3), 909-916, **2008**.

52) Sinko P. J. Martin's physical pharmacy and pharmaceutical sciences, 5th edition, Lippincott Williams & Wilkins, New York, 523-558, **2008**.

53) S. Jayaprakash, S. Mohamed Halith, K.Kulathuran Pillai, Priya Balasubramaniyam, P. U. Mohamed Firthouse and M. Boopathi. Formulation and evaluation of bilayer tablets of amlodipine besilate and metprolol succinate S. Der Pharmacia Lettre, 3 (4), 143-154, **2011**.

54) Sonara GS, Jain DK and More DM. Preparation and *in vitro* evaluation of bilayer and floating bioadhesive tablets of rosiglitazone maleate, *Asian J. Pharma. Sci*, 2(4), 161-169. **2007**.

55) **Stephen D. Silberstein.** Trends in Pharmacological Sciences, 27(8), 410-415, **2006**.

56) Sweetman SC (Eds), Martindale. The complete drug reference, 33rd edition, Great Britain, Pharmaceutical press, 456-458, **2002**.

57) Turner S, Federici C, Hite M and Fassihi R. Formulation development and human *in vitro-in vivo* correlation for a novel, monolithic controlled release matrix system of high load and highly water-soluble drug niacin, Drug Development and Industrial Pharmacy, 30, 797-807, **2004**.

58) Vogeleer J. Bilayer tablets – why special technology required, The courtoy R292F tablet press, designed for quality bilayer tablets, 1(1), 1-6, **2002**.

59) Yellanki SK, Bigala R, Jawad ali syed, Deb SK and Goranti S. Design and *in vitro* evaluation of mucoadhesive minitablets for nasal drug delivery of sumatriptan succuinate, *Asian J Pharma Clin Res*, 3(3), 218-220, **2010**.

60) Yie WC. Novel drug delivery systems, 2nd edition, Madison Avenue (NY), Marcel Dekker, Inc, **1992**.